5-HT$_{1C}$ receptors and th ir therapeutic relevance

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Introduction

Considerable advances have been made in the understanding of 5-hydroxytryptamine (5-HT) receptor pharmacology in the last decade. In 1979 the existence of more than one 5-HT receptor binding site was recognised for the first time when [3H]lysergic acid diethylamine (LSD) binding in the rat cortex was found to contain 5-HT and spiperone (Janssen, Figure 1) sensitive components [1]. The 5-HT sensitive component was described as 5-HT$_1$ and the spiperone sensitive portion 5-HT$_2$. Subsequently Pedigo *et al.* [2] showed that at least two 5-HT$_1$ receptors existed, since high affinity [3H]5-HT binding was partially displaced by spiperone. These putative receptor subtypes were termed 5-HT$_{1A}$ (spiperone sensitive) and 5-HT$_{1B}$ and can be more specifically labeled by [3H]8-hydroxy-2-di-n-propylamino-tetralin (8-OH-DPAT) [3,4] and [125I]iodocyanopindolol [5] respectively. Subsequently 5-HT$_{1C}$ [6] 5-HT$_{1D}$ [7], 5-HT$_{1E}$ [8], 5-HT$_3$ [9,10] and 5-HT$_4$ [11] receptors have been identified.

The 5-HT$_{1C}$ receptor

5-HT$_{1C}$ receptor binding studies

One area found to contain 5-HT$_1$ binding sites by autoradiographic studies was the rat choroid plexus [12]. However these '5-HT$_1$' receptors were found to bind [3H]mesulergine (Sandoz, Figure 1), a putative 5-HT$_2$ receptor ligand [13], but not the 5-HT$_2$ specific ligand [3H] ketanserin (Janssen, Figure 1) [14,15]. The 5-HT$_{1A}$ ligand 8-OH-DPAT and 5-HT$_{1B}$ ligand RU 24969 (Roussel UCLAF) also failed to displace [3H]mesulergine binding from this site which was therefore termed the 5-HT$_{1C}$ receptor [6]. The pharmacology of this receptor has a considerable similarity to that of the 5-HT$_2$ receptor. Thus most 'classical' 5-HT$_2$ receptor antagonists such as mianserin (Organon, Figure 1) and methysergide (Sandoz), are unable to discriminate between the two sites. Exceptions include ketanserin (Janssen, Figure 1), altanserin (Janssen), pirenperone (Janssen), and spiperone, all of which show selectivity for the 5-HT$_2$ receptor [16] as do two recently developed compounds RP 62203 (Rhone Poulenc, Figure 1) [17] and SR 46349B (Sanofi) [18] (Table 1). 5-HT$_2$ receptor agonists are also largely non-selective; indeed only a few compounds, whether agonist or antagonist, show selectivity for the 5-HT$_{1C}$ over the 5-HT$_2$ site (Table 1). These include 1-methyl 5-HT (one hundred-fold selective), MK 212 (Merck Sharp & Dohme, Figure 2; fifty-fold selective), (+)3-(2-aminopropyl)benz[e]indole hydrochloride (thirty-three-fold selective) [19], 1-naphthyl piperazine (1-NP) (ten-fold selective), 1-(3-chlorophenyl) piperazine (mCPP, Figure 2; ten-fold selective) and LY 53857 (Lilly; six-fold selective). 5-HT$_{1C}$ receptors have been pharmacologically characterized in pig and human choroid plexus tissue and rat cortex. There were only minor differences in the affinities of the thirteen compounds tested [20].
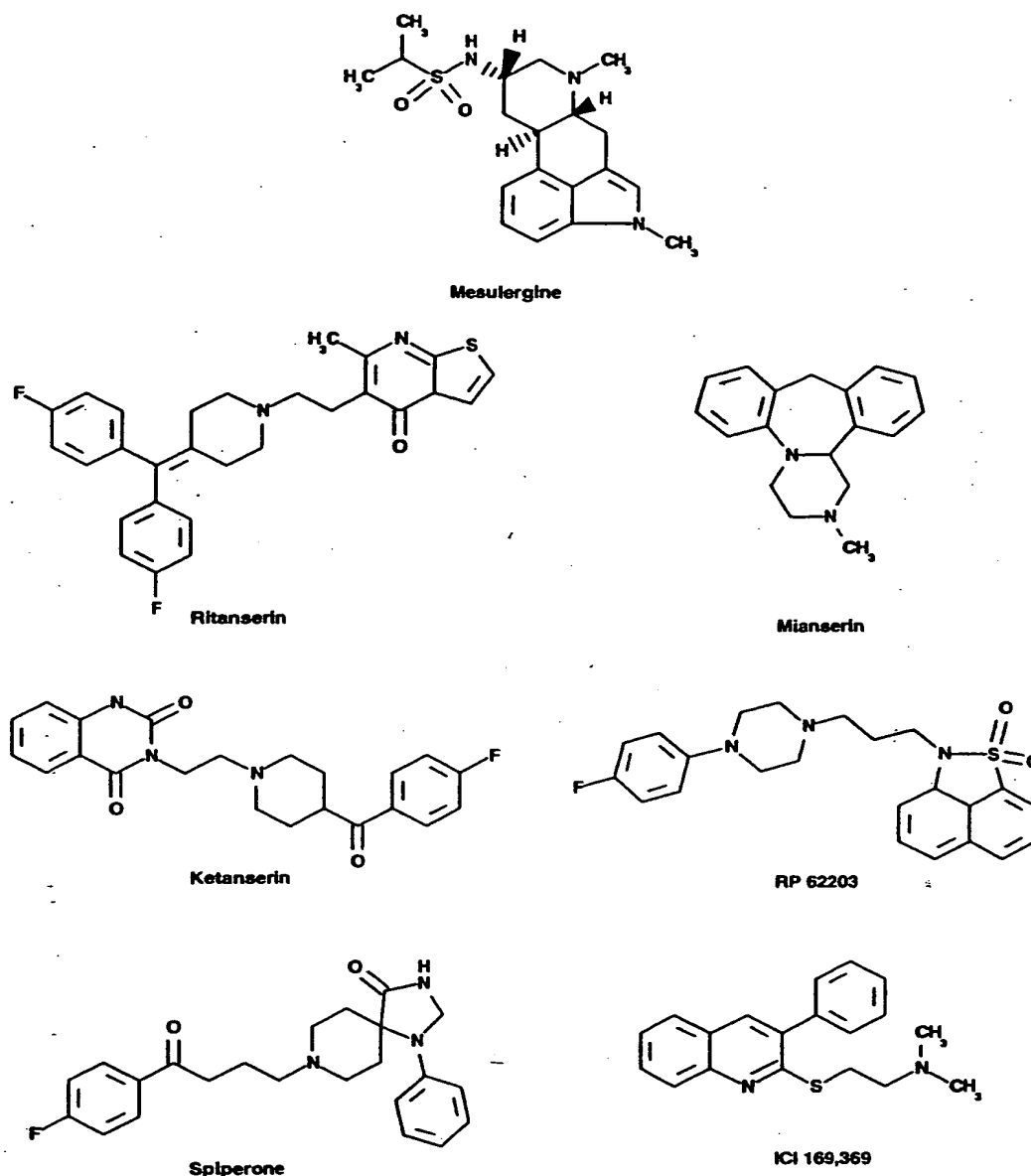
Figure 1: 5-HT$_{1C}$/5-HT$_2$ receptor antagonists

Several non-selective 5-HT$_2$/5-HT$_{1C}$ receptor antagonists have been used clinically and many of the arguments advanced in the present review are based on their actions. Of these ICI 169,369 (Figure 1) and ICI 170,809 have the 'cleanest' profile. ICI 169,369 has thirteen-fold selectivity over the adrenergic α_1 receptor (Table 1). ICI 170,809 has twenty-fold higher affinity for 5-HT$_{1C}$ site over the dopamine D$_2$ site and sixty-three-fold selectivity over the adrenergic α_1 receptor and one hundred-fold higher affinity for 5- HT$_{1C}$ over the histamine H$_1$ site (Table 1). Ritanserin (Figure 1) has also been widely used clinically but has only three-fold selectivity for the 5-HT$_{1C}$ over the H$_1$ receptor and only ten-fold over the adrenergic α_1 site. It also has high affinity for dopamine D$_2$ receptors (Table 1). Lastly mianserin is equipotent at 5-HT$_{1C}$, 5-HT$_2$ and H$_1$ receptors, has six-fold selectivity over 5-HT$_3$ and sixteen-fold selectivity over adenergic α_2 sites (Table 1). Clearly none of the above drugs is an ideal tool for the study of 5-HT$_{1C}$ receptor function.

Even fewer agonists have been used, but one, mCPP, is discussed in some detail later. One problem with the interpretation of human data derived from the use of these drugs is that their affinities for human receptors may differ from their rat equivalents. One example of this is the fifty-fold higher affinity that mesulergine has for rat as opposed to human 5-HT$_2$ receptors [21]. This may give mesulergine a fifty-fold greater affinity for the 5-HT$_{1C}$ over the 5-HT$_2$ receptor in humans. In the same study ritanserin had a seven-fold lower affinity for rat than for human 5-HT$_2$ sites.

Table 1: Affinity values of 5-HT$_{1C}$ receptor antagonists for 5-HT, adrenergic α_1 and α_2, dopaminergic D$_2$ and histamine H$_1$ receptors in mammalian brain membranes.

Drug	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1C}$	5-HT$_{1D}$	5-HT$_2$	5-HT$_3$	α_1	α_2	D$_2$	H$_1$
1-NP	7.2	6.6	8.3	7.8[b]	7.2	6.9	-	-	-	-
LY 53857	6.4	5.5	8.1	-	7.3	7.5[f]	-	-	-	-
Mesulergine	6.2	4.9	8.8	5.2	8.4	-	5.3[b]	6.1[b]	6.8[b]	5.2[b]
ICI 169,369	5.3	-	8.0[c]	6.3	7.8[d]	6.0[c]	6.2[d]	5.9[d]	6.9[d]	6.0[d]
ICI 170,809	<6.0[g]	-	8.3[f]	-	9.1[g]	-	7.0[g]	-	6.1[g]	6.3[g]
Metergoline	8.1	7.4	9.2	8.3	9.0	-	7.0[a]	6.0[a]	7.2[a]	5.7[a]
Ritanserin	5.2	<4.0	8.9	5.8	8.8	5.6[g]	7.9[g]	7.1[g]	7.5[g]	8.4[g]
Methysergide	7.6	5.8	8.6	8.4	8.6	4.5	5.2[a]	5.2[a]	6.3[a]	<6.0[a]
Mianserin	6.0	5.2	8.0	6.4	8.1	7.2	6.6[a]	6.8[a]	5.8[a]	8.3[a]
SR 46349B	4.9[i]	4.8i	6.9[i]	<6.0[i]	8.2[i]	-	5.5[i]	6.0[i]	<6.0[i]	5.3[i]
RP 62203	7.1[g]	<6.0[g]	8.5[f]	-	9.9[g]	5.2[g]	8.4[g]	<6.0[g]	6.4[g]	7.3[g]
Setoperone	5.6	5.3	7.3	-	8.6	-	-	-	-	-
Pirenperone	5.9	5.3	7.3	-	8.8	-	-	-	-	-
Altanserin	5.6	6.0	6.9	-	8.6	-	-	-	-	-
Cisapride	5.7	5.2	6.3	5.3	8.1	-	-	-	-	-
Ketanserin	5.9	5.7	7.0	6.0	8.9	3.6	7.5[a]	<6.0[a]	6.3[a]	7.7[a]
Spiperone	7.2	5.3	5.9	5.3	8.8	3.6	-	-	-	-

Data taken from [16] or [423] except:

[a] Ref [15]	[b] Ref [62]	[c] Ref [100]
[d] Ref [250]	[e] Ref [103]	[f] Wood MD, personal communication
[g] Ref [17]	[h] Ref [13]	[i] pIC$_{50}$ values from [18]

The 5-HT$_{1C}$ receptor secondary messenger system

Palacios *et al.* [22] reported that activation of 5-HT$_{1C}$ in the pig choroid plexus had no effect on adenylate cyclase activity. However 5-HT was found to cause the stimulation of phospholipase C and the breakdown of phospholipids in homogenates of this tissue [23], actions usually associated with the release of Ca^{2+} ions from the intracellular stores [24,25]. This effect was potently inhibited by the non-selective 5-HT$_{1C}$/5-HT$_2$ receptor antagonist mianserin but only by high concentrations of the selective 5HT$_2$ receptor antagonist [16] ketanserin and spiperone [23], suggesting 5-HT$_{1C}$ receptor mediation. Subsequently Hoyer *et al.* [26] correlated the potency of twelve agonists and fourteen antagonists in inducing or inhibiting 5-HT-induced phosphoinositide (PI) hydrolysis in choroid plexus cells, with their

affinities for the 5-HT$_{1C}$ receptor. Since 5-HT$_2$ receptors are also coupled to a PI hydrolysis secondary messenger system this is another common feature of the two receptors.

5-HT$_{1C}$ receptor stimulation may also result in activation of Cl$^-$ channels. Application of 5-HT to Xenopus oocytes injected with rat brain or choroid plexus messenger ribonucleic acid (mRNA) causes PI hydrolysis and increased intracellular Ca^{2+} levels. This in turn was shown to cause the opening of Ca^{2+}-dependent Cl$^-$ channels [27-30]. The pharmacology of Cl$^-$ ion channel activation by 5-HT in this system is most consistent with 5-HT$_{1C}$ receptor mediation [28,29]. However there are several discrepancies such as the relatively high affinity of ketanserin and low affinity of cyproheptadine (Merck Sharp & Dohme) and mesulergine compared to that determined by receptor binding [16,28]. In Xenopus oocytes expressing mRNA from rat brain the effect of 5-HT on Cl$^-$ currents was mimicked by the intracellular application of guanosine triphosphate α (GTP)-γ-S. Both effects were blocked by injection of the Ca^{2+} chelator ethylene glycol-bis(β-aminoethyl ether) N,N,N,N-tetraacetic acid (EGTA). The effect of 5-HT was also blocked by pertussis toxin which was shown to promote the adenosine diphosphate (ADP)-ribosylation of a GI-protein [31]. This data suggests that a Ca^{2+} dependent Cl$^-$ ion channel is activated via a G-protein stimulation of phosphoinositide hydrolysis. 5-HT mediated stimulation of ion channels has also been observed in oocytes expressing mRNA from both human brain [27] and rat small intestine [32], although no pharmacological analysis was made. It remains to be seen whether 5-HT$_{1C}$ receptors in the brain are coupled to Cl$^-$ channels, or whether this coupling is artificially created by the expression of mRNA in an alien cell and its endogenous inositol phospholipid signalling system.

Evidence from Xenopus oocytes injected with both rat brain 5-HT$_{1C}$ receptor and K$^+$ channel mRNA, suggests that 5-HT$_{1C}$ receptors may modulate the function of K$^+$ channels. Thus in the presence of EGTA to suppress Cl$^-$ ion channel activation, 5-HT causes an inward current, not found in oocytes injected with either mRNA alone [33], which is due to the closing of a class of K$^+$ channels [34,35].

5-HT$_{1C}$ receptor molecular biology

The 5-HT$_{1C}$ receptor was first cloned by Lubbert *et al.* [29] from rat choroid plexus tissue. The method used involved isolating rat choroid plexus mRNAs, fractionating them by gel electrophoresis and expressing them in Xenopus oocytes where stimulation of the 5-HT$_{1C}$ receptor, formed from the desired mRNA, results in Cl$^-$ ion channel opening. The mRNA thus identified had a molecular weight of 5000 daltons. Later Julius *et al.* [36] published the amino acid sequence of this receptor which contained 460 residues. The sequence revealed seven regions of hydrophobicity each of 20-30 amino acids. These regions would be expected to associate with the hydrophobic lipid membrane to form helical transmembrane domains. This arrangement is common to all members of the G protein-coupled receptor family of membrane proteins which include the 5-HT$_2$, 5-HT$_{1A}$, adrenergic β receptor and muscarinic acetylcholine receptors amongst others. The family is so called because the response to receptor activation is indirectly mediated by a class of GTP-hydrolysing enzymes allosterically coupled to the receptor. Thus receptor stimulation activates a G protein which in turn acts upon the cellular system [37]. A more recent study has suggested that the 5-HT$_{1C}$ receptor in rat and mouse have an eighth transmembrane domain not found in other members of the G protein-coupled family [38]. Human 5-HT$_{1C}$ receptor sequences have also been recently reported [39]. Both mouse and human sequences are very similar to the rat, the mouse amino acid sequence having 97% [38] and human 90% [39] homology. These small differences have not yet been observed to have great pharmacological significance.

One observation from the sequencing of the 5-HT$_{1C}$ receptor was its resemblance to the 5-HT$_2$ receptor. In rat the overall homology is 51% as opposed to 35% for the 5-HT$_{1A}$ receptor. When the seven transmembrane domains are compared this rises to 79% homology for the 5-HT$_2$ receptor [40]. In humans total 5-HT$_2$ and 5-HT$_{1C}$ gene sequence homology was 50% and in transmembrane domains 80% [39].

It is of some interest that the 5-HT$_{1C}$ receptor gene is located on the X chromosome, unlike 5 HT$_2$ or 5-HT$_{1A}$ receptors [38]. This suggests that it may be involved in the effects of 5-HT on sexual differentiation [41].

5-HT$_{1C}$ receptor distribution

Autoradiographic studies using [^{3}H]mesulergine in rat brain have demonstrated very high densities of 5-HT$_{1C}$ receptor binding sites in the choroid plexus with roughly ten-fold lower densities in the hippocampus CA1 region, substantia nigra, globus pallidus, layer III of the cerebral cortex, olfactory cortex, lateral amygdaloid nucleus and thalamus [42]. This distribution is paralleled in mice [43]. A more detailed study of the human brain has also revealed a similar distribution. Here low levels were widely distributed in the following rank order of density: hypothalamus ventromedial nucleus > globus pallidus > hippocampus CA1 and CA3 > substantia nigra, nucleus accumbens, putamen > amygdala > thalamus. Other regions contained even lower densities [20,44].

One problem with the mapping of 5-HT$_{1C}$ receptors is the high level of non-specific binding encountered with [^{3}H]mesulergine [44]. The mapping of 5-HT$_{1C}$ mRNA is more specific and has allowed improved accuracy. Several studies have been conducted. In general these have confirmed receptor binding distributions. However some discrepancies have emerged, particularly the relatively high densities of mRNA in the septum, lateral habenula and subthalamic nucleus which are not matched by high levels of binding [43,45]. These may suggest differences in regional receptor turnover rates or reflect transport of mRNA from the cell body site of synthesis to the site of expression. Some discrepancies may be due to experimental differences. Thus Hoffman & Mezey [45] report high 5-HT$_{1C}$ mRNa levels in rat dentate gyrus not seen by Molineaux et al. [46] or Mengod et al. [43], while Molineaux et al. [46] report high levels in the hippocampal CA1 region which were not seen by Hoffman & Mezey [45] or Mengod et al. [43].

The existence of 5-HT$_{1C}$ receptors outside the brain has yet to be demonstrated. Only one model has been proposed: mediation of 5-HT-induced contractions of the rat stomach fundus [47]. This rests on the antagonist potency in this model of the older 5-HT$_{1C}$/5-HT$_2$ receptor antagonists such as mianserin, methysergide and pizotifen (Sandoz) but not specific 5-HT$_2$ receptor antagonists [48,49]. However there are a number of differences. Yohimbine and rauwolcine, which are also potent antagonists of 5-HT in the fundus [48], have little affinity for the 5-HT$_{1C}$ receptor [16]. Also many 5-HT$_{1C}$/5-HT$_2$ receptor antagonists act as non-surmountable antagonists [48] making predictions of affinity difficult. Furthermore 5-HT stimulation of the fundus appears not to cause PI hydrolysis [50]. No 5-HT$_{1C}$ mRNA was detected in the tissue [51] while extracted mRNA expressed in Xenopus oocytes inhibited cyclic adenosine monophosphate (CAMP) formation [52]. Recently Foquet et al. [53] reported that the rat stomach fundus gene is closely related to, but structurally distinct from, the 5-HT$_2$ and 5-HT$_{1C}$ receptor genes. This receptor was not observed in brain tissue in further studies by this group [54].
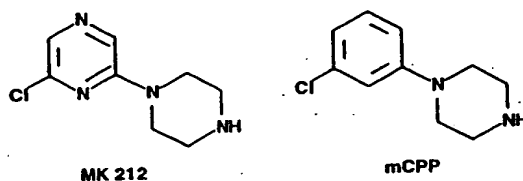
The expression of 5-HT_{1C}-like receptors from rat small intestine mRNA injected into oocytes [32] suggests that peripheral 5-HT_{1C} receptors may exist. 5-HT_{1C} receptor mediation of penile erections in rats, however, is likely to be centrally mediated [55].

MCPP - a putative 5-HT_{1C} agonist

MCPP is a metabolite of the widely prescribed antidepressant trazodone (Bristol-Myers Squibb) [56]. For this reason it has been considered ethical to administer the drug to humans. MCPP has principally been considered a 5-HT_{1B} agonist since it reduces 5-HT release in brain slices [57] and was observed to displace supposed 5-HT_{1B} receptor binding [58], although the preparation used would have contained 5-HT_{1C} receptors as well. In 1988 two prominent behavioural effects of mCPP, hypolocomotion [59] and hypophagia [60], were reported to be caused by 5-HT_{1C} receptor stimulation. This was consistent with receptor binding studies in which the drug had at least ten-fold selectivity over other 5-HT receptor subtypes including $5\,\text{HT}_{1B}$ sites (Table 2). It was also consistent with the ability of mCPP to stimulate PI hydrolysis in the rat choroid plexus [61]. In this paradigm mCPP is reported to act with 65 to 90% of the efficacy of 5-HT whether rat [61] or pig [62,63] tissue is used, although both preparations have little receptor reserve [63,64]. MCPP's selectivity as a 5-HT_{1C} agonist is enhanced by its actions as a silent antagonist at cortical 5-HT_2 receptors mediating PI hydrolysis [61], in the 5-HT_2-mediated head twitch model in rats [65, 66] and in the 5-HT_2-mediated rat jugular vein model [67]. It is also an antagonist of rat vagus nerve [10] and rat cardiac [68] 5-HT_3 receptors. Against bovine 5-HT_{1D} receptors, Schoeffter & Hoyer [62] reported that it was a weak (30%) partial agonist with an estimated pK_B of 5.1. This was somewhat less than its binding affinity for the site; $pK_I = 5.8\text{--}5.9$ (Table 1). Recently two $5\,\text{HT}_{1D}$ receptor subtypes have been identified $5\text{-HT}_{1D\alpha}$ and $5\text{-HT}_{1D\beta}$ [69]. The affinity of mCPP for cloned human $5\text{-HT}_{1D\alpha}$ and $5\text{-HT}_{1D\beta}$ receptors is reported to be 6.6 and 6.4 respectively [69]. The slightly higher affinity of mCPP for these cloned human 5-HT_{1D} receptors may reflect species differences or conceivably an artifact. MCPP has little affinity for 5-HT_{1E} or 5-HT_4 receptors.

The ten-fold selectivity of mCPP for 5-HT_{1C} over 5-HT_{1B} receptors evidenced by binding studies was not observed in a comparision of its efficacy in stimulating their respective secondary messengers [62] (Table 2) although selectivity over 5-HT_{1A}, 5-HT_{1D} and 5-HT_2 receptors was largely maintained. This was due to a large proportion of agonists tested having pEC_{50} values in the 5-HT_{1C} PI hydrolysis test roughly ten-fold lower than their binding affinities [26,62]. Since the degree of amplification needed to evoke a physiological or behavioural response in the different systems is unknown the relevance of this finding it unclear. Furthermore its relevance to mCPP's effects in man is also unclear. While 5-HT_{1B} receptors are not widely distributed in human tissue [44], a species homologue, the $5\text{-HT}_{1D\beta}$ receptor, is found [69]. At the present time no data as to the effects of mCPP on this receptor's secondary messenger systems has been reported.

MCPP has also been reported to have some affinity for the adrenergic α_2 receptor ($pK_D = 6.2$) [70]. This is approximately forty-fold less potent than its affinity for 5-HT_{1C} receptors [62], although whether mCPP acts as an agonist or antagonist at these sites is unknown. Another ambiguity is the reported release of 5-HT *in vitro* by mCPP [71]. The importance of this effect has yet to be clarified but implies that intact presynaptic serotonergic function would be necessary to sustain an effect of mCPP mediated in this way. MCPP has very weak affinity for the adrenergic α_1 and β receptors, and for the dopamine D_2, muscarinic and benzodiazepine receptors [72].

MK 212   **mCPP**

Figure 2: 5-HT$_{1C}$ agonists

Table 2: Profile of the *in vitro* actions of mCPP

Receptor	Affinity of mCPP		Functional model		
	Rat or Pig (pK$_i$ or pK$_D$)	Human (pIC$_{50}$)	Model	pEC$_{50}$ (pK$_B$ or pA$_2$)	Efficacy (%)
5-HT$_{1A}$	6.6[a]	6.4[b]	Adenylate cyclase	5.9	40[c]
5-HT$_{1B}$	6.5[a]		Adenylate cyclase	6.5	60[c]
5-HT$_{1C}$	7.8[a]		Phosphoinositide hydrolysis	6.9	65[c]
	7.4[d]			7.1	90[d]
5-HT$_{1D}$	5.8[a]	5.9[b]	Adenylate cyclase	5.1	30[c]
5-HT$_{1D\alpha}$	6.6[i]				
5-HT$_{1D\beta}$	6.4[i]				
5-HT$_{1E}$	5.0[j]				
5-HT$_2$	6.7[a]	6.6[b]	Phosphoinositide hydrolysis	6.1**	0[c]
5-HT$_3$	7.0[a]		Vagus nerve	6.6***	0[b]
5-HT$_4$	5.0[j]				
α_1 adrenoceptor		5.5[b]			
α_2 adrenoceptor	6.2[f]	6.2[b]			
β adrenoceptor		5.6[b]	—		
Dopamine D$_1$		5.1[b]			
Dopamine D$_2$		5.0[b]			
Benzodiazepine	< 4.0[b]				
5-HT reuptake	< 4.0[b]				
5-HT release	0.1-1mM*[g]				

*   Minimum effective dose
**   pK$_i$
***pA$_2$

Data taken from:

[a] [16]   [b] [72]   [c] [62]   [j] [AM Brown, personal communication]
[d] [63]   [e] [61]   [f] [70]
[g] [71]   [b] [10]   [i] [69]

In conclusion, mCPP is a 5-HT$_{1C}$ receptor agonist and may have some selectivity for the site. In humans this selectivity may be promoted by the apparent absence of the 5-HT$_{1B}$ receptor although this may be offset by the higher affinity of the drug for cloned human 5-HT$_{1D\alpha}$ and 5-

$HT_{1D\beta}$ receptors [44]. The effects of mCPP in man have greatly contributed to perceptions of the utility of $5-HT_{1C}$ receptor ligands.

Table 3: Behavioural effects of mCPP in rats: models f $5-HT_{1C}$ receptor function?

Paradigm	Antagonist	Dose mg/kg, *ip/sc*	Receptor Selectivity	Effect [Reference]
Hypolocomotion	Metergoline	1-5	$5-HT_1$, $5-HT_2$	Blocks[b,c] [59,229,235,426,427]
	Methysergide	5-10	$5-HT_1$, $5-HT_2$	Blocks[b,c] [427]
	Mianserin	2	$5-HT_{1C}$, $5-HT_2$, α_2	Blocks[b,c] [59,427]
	Cyproheptadine	2	$5-HT_{1C}$, $5-HT_2$, H_1	Blocks [59] / No effect[b] [427]
	Mesulergine	0.5-4	$5-HT_{1C}$, $5-HT_2$	Blocks[b] [427]
	Ketanserin	0.2-1	$5-HT_2$	No effect[c] [59,426]
	Ritanserin	0.1-2	$5-HT^a_2$	No effect[b] [59,426,427]
	Spiperone	0.01-0.05	$5-HT_2$, D_2	No effect?[b] [427]
	Cyanopindolol	0.2-8	$5-HT_{1A}$, $5-HT_{1B}$, β	No effect[b] [59,427]
	Pindolol	2	$5-HT_{1A}$, $5-HT_{1B}$, β	No effect[c] [59]
	Propranolol	5-16	$5-HT_{1A}$, $5-HT_{1B}$, β	No effect[c] [59] / Potentiates [235]
	ICS 205,930	1	$5-HT_3$	No effect [59,427]
	MDL 72,222	0.5	$5-HT_3$	No effect [426]
	Idazoxan	1	α_2	No effect [59,427]
	PCA	Chronic	5-HT lesion	Blocks [427]
	PCPA	Chronic	5-HT depletion	No effect [Unpublished observation]
Hypophagia	Metergoline	1-5	$5-HT_1$, $5-HT_2$	Blocks[d] [60,428,429]
	Mianserin	2-5	$5-HT_{1C}$, $5-HT_2$ α_2	Blocks[d] [60]
	Cyproheptadine	10	$5-HT_{1C}$, $5-HT_2$ H_1	No effect [60]
	Mesulergine	0.2	$5-HT_{1C}$, $5-HT_2$	Blocks[d] [60]
	Ketanserin	0.2	$5-HT_2$	No effect[e] [60]
	Ritanserin	0.6	$5-HT_2$[a]	No effect[e] [60]
	Cyanopindolol	8	$5-HT_{1A}$, $5-HT_{1B}$ β	Blocks[e] [60]
	Propanolol	16	$5-HT_{1A}$, $5-HT_{1B}$ β	Blocks [60]
	ICS 205,930	1	$5-HT_3$	No effect [60]
	Idazoxan	1	α_2	No effect [60]
	Median Raphe lesion		Lesion	No effect [428]

Table 3: (cont.)

Paradigm	Antagonist	Dose mg/kg, *ip/sc*	Receptor Selectivity	Effect [Ref rence]
Penile Erection	Metergoline	0.02-0.2	5-HT$_1$, 5-HT$_2$	Blocks [231]
	Mianserin	0.02-0.2	5-HT$_{1C}$, 5-HT$_2$ α$_2$	Blocks [231]
	Cyproheptadine	0.1-1.0	5-HT$_{1C}$, 5-HT$_2$ H$_1$	Blocks [231]
	Mesulergine	0.02-0.2	5-HT$_{1C}$, 5-HT$_2$	Blocks [231]
	Ketanserin	0.5-1.0	5-HT$_2$	No effect [231]
	Ritanserin	0.1-0.5	5-HT$_2$ ª	Blocks [231]
	Spiperone	0.1-1.0	5-HT$_2$, D$_2$	No effect [231]
	GR 38032F	1-10	5-HT$_3$	No effect [231]
Hyperthermia	Metergoline	0.5	5-HT$_1$, 5-HT$_2$	Blocks [233]
	Ritanserin	0.6ª	5-HT$_2$	No effect [233]
	Pindolol	4	5-HT$_{1A}$, 5-HT$_{1B}$ β	No effect [233]
	Propanolol	6	5-HT$_{1A}$, 5-HT$_{1B}$ β	No effect [233]
Purposeless Chewing	Mianserin	1	5-HT$_{1C}$, 5-HT$_2$	Blocks [431]
	Ketanserin	5	5-HT$_2$	No effect [431]
	Spiperone	0.5	5-HT$_2$, D$_2$	No effect [431]
	ICS 205,930	10	5-HT$_3$	No effect [431]
	(–)Propranolol	20	5-HT$_{1A}$, 5-HT$_{1B}$ β ^{f}	Blocks [431]

ª Since the *in vivo* ID$_{50}$ value for ritanserin against mCPP-induced hypophagia was 4.6 mg/kg *sc* [66], doses below this may be 5-HT$_2$ selective.

b/c Similar results obtained against TFMPP-induced hypolocomotion. Results from ^{b} [427] and ^{c} [229].

d Similar results obtained against TFMPP-induced hypophagia in freely feeding rats [430].

e Ketanserin 2.5 mg/kg partially blocked, cyanopindolol had no effect and ritanserin 0.5 and 1 mg/kg *ip* had an inverse dose related effect on TFMPP-induced hypopgagia [430].

f As (-)propranolol does not have pronounced specificity for 5-HT$_{1A}$ and 5-HT$_{1B}$ over 5-HT$_{1C}$ sites [16], this dose may have blocked them all.

Possible therapeutic targets of 5-HT$_{1C}$ receptor ligands:

Anxiety

Anxiety is widely observed in nearly all forms of mental illness. It is present in its purest form in anxiety disorders but is a noted feature of depression, schizophrenia and personality disorders. Four major types of anxiety have been characterised; generalised anxiety disorder (GAD), panic disorder with or without agorophobia, obsessive compulsive disorder (OCD), and other phobias. Several problems are associated with existing therapy. One of the most serious is the development of dependence in patients on long term benzodiazepine treatment. This leads to the induction of a marked anxiety on withdrawal [73]. Other problems include sedation and the interaction of this class of drugs with alcohol and barbiturates. Furthermore benzodiazepines are ineffective in the treatment of OCD [74], which only responds to chronic treatment with some antidepressants [75] and is then only partly effective. Chronic

antidepressant treatment is also efficacious in panic disorder [76-78]. However the side effect profile of this class of drugs (which includes anticholinergic, sedative and postural hypotensive effects for tricyclic antidepressants and hypotension and insomnia for monoamine oxidase inhibitors (MAOI)) has prevented their widespread use in these indications. Even the selective 5-HT reuptake inhibitor (SSRI) fluoxetine (Lilly) is associated with insomnia, nausea and asthenia [79].

Generalised anxiety disorder

Administration of mCPP to human volunteers caused anxiety [80-84]. In some subjects panic attacks were experienced [84,85]. The anxiogenic response to mCPP is accompanied by an increase of the stress sensitive hormones adrenocorticotrophic hormone (ACTH), cortisol and prolactin [80,86,87]. However there is some uncertainity over whether the hormonal changes are secondary to anxiety or not. Two studies of prolactin release suggest that it does follow peak anxiety [81,86] while one does not [84], although significant anxiety was not seen in this study.

MCPP administration to rats also induces anxiogenic-like responses in both the social interaction (SI) [88,89] and the elevated X-maze [Kennett, unpublished observations] models of anxiety, and decreases punished responding in a pigeon conflict model [90]. However in both the rat Geller-Seifter [91] and acoustic startle [92] models of anxiety the actions of mCPP were obscured by sedative or motor effects.

The anxiogenic response to systemic mCPP in the SI test was replicated after intra-hippocampal, but not intra-amygdaloidal, infusion [89]. This region has long been associated with the control of anxiety and is known to contain 5-HT$_{1C}$ receptors [42,43,45,46]. The effect of mCPP, at least in the elevated X-maze, is not secondary to the release of 5-HT as it is not opposed by pretreatment with the 5-HT synthesis inhibitor p-chlorophenylalanine [Kennett, unpublished observations].

The pharmacology of the anxiogenic responses to mCPP in the rat SI and elevated X-maze tests is consistent with 5-HT$_{1C}$ mediation. Thus in the SI test it is blocked by the non specific 5-HT$_2$/5-HT$_{1C}$ receptor antagonists mianserin, cyproheptadine and metergoline (Farmitalia) (Table 1) but not by the selective 5-HT$_2$ antagonist ketanserin (Table 1) or by the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor antagonists [16] cyanopindolol (Sandoz) and (-)propranolol (ICI) [88]. The action of mCPP in the X-maze was similarly opposed by the non-selective 5-HT$_2$/5-HT$_{1C}$ receptor blockers mianserin, LY 53857 and 1-NP [16], but not by the selective 5-HT$_2$ antagonists ketanserin and altanserin [16] nor by the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor blockers pindolol (Sandoz) [16] and cyanopindolol [Kennett, unpublished observations]. The effects of mCPP in both models was opposed by the benzodiazepine anxiolytic chlordiazepoxide (Roche) [88,93] reinforcing the interpretation that mCPP is anxiogenic. The anxiogenic effects of mCPP in both models were also attenuated by the 5-HT$_3$ receptor antagonists [16,94] ICS 205,930 (Sandoz) [88] and BRL 46470A (SmithKline Beecham) [93] in the SI and X-maze tests respectively. This is likely to be caused by the anxiolytic profile of these drugs [93,95]. Indeed mCPP might have more pronounced anxiogenic activity if it had less affinity for the 5 HT$_3$ site at which it is an antagonist (Table 1).

The results from rat models are consistent with the available clinical data. Thus the anxiogenic responses to mCPP have been reported to be blocked by the non-selective 5-HT$_1$ and 5-HT$_2$ receptor antagonists metergoline [85,96] and methysergide [85] and by the 5-HT$_2$/5-HT$_{1C}$ receptor antagonist ritanserin (Janssen) [83]. This last report is of considerable interest, as

ritanserin has little affinity for other 5-HT receptor subtypes [16] and mCPP itself is a 5-HT$_2$ antagonist (see section on mCPP as a putative 5-HT$_{1C}$ agonist).

The effects of antagonists on neuroendocrine responses to mCPP are similar. Metergoline and ritanserin both attenuate mCPP-induced prolactin secretion [83,87,96,97]. They also blocked the increase in cortisol [83,87,97]. Metergoline blocks the ACTH response as well [87]. Methysergide, however, was reported to block prolactin but not cortisol responses to mCPP [97].

Mediation of the anxiogenic effects of mCPP by 5-HT$_{1C}$ receptor activation suggests that their blockade would be anxiolytic provided that some tone is exerted through the receptors under normal and/or anxiety provoking conditions. This hypothesis is supported by evidence from animal studies. In two recent studies [98,99], five non-selective 5-HT$_2$/5-HT$_{1C}$ receptor antagonists, mianserin, 1-NP, ICI 169,369 (ICI), LY 53857 and pizotifen, (Table 1, [16,100]), were found to have anxiolytic-like actions in both the SI and Geller Seifter conflict tests. Compounds that did not share this property include: the selective 5-HT$_2$ antagonists ketanserin and altanserin, (Table 1); 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor antagonists pindolol and cyanopindolol [16]; adrenergic α_2 receptor antagonist idazoxan (Reckitt and Colman) [101] or adrenergic α_2 antagonist and 5-HT$_{1D}$ partial agonist yohimbine [101,102]; and H$_1$ antagonist mepyramine (May and Baker). The possibility of 5-HT$_3$ mediation of the effects is also unlikely as ICI 169, 369 [103] and LY 53857 (Table 1) have low affinity for this site, and 5-HT$_3$ antagonists are inneffective in the Geller-Seifter test [104,105]. Since the two tests have different motivational and aversive components the conclusion that these non-selective 5-HT$_{1C}$ receptor antagonists are anxiolytic is strengthened. Similar findings have not been universally reported. The 5-HT$_2$/5-HT$_{1C}$ receptor antagonist ritanserin, for instance, was inactive in one SI test [106], although the conditions used were inappropriate for the detection of anxiolysis [98]. The compound was active in one rat conflict procedure [107] but not in three others [108,109], although the paradigms used in the latter study were insensitive to benzodiazepines also. However, in the pigeon conflict test, claimed to be more sensitive to serotonergic drugs, ritanserin has shown an anxiolytic profile [90,109]. Mianserin, too, had no effect on SI where relatively high doses were used [110] but was active in the Geller-Seifter test when lower doses, similar to those of Kennett [98] or Kennett et al. [99], were used [111]. Another 5-HT$_2$/5-HT$_{1C}$ receptor antagonist cyproheptadine [16] was also effective in some [112,113] but not all [108] conflict tests, while ICI 169,369 had some activity in the pigeon conflict test [114]. The non-specific 5-HT$_1$ and 5-HT$_2$ antagonists methysergide and metergoline [16] were not active in the SI test, albeit under different conditions [115], but were active in conflict tests [116-120]. The selective 5-HT$_2$ receptor antagonist ketanserin has also shown an anxiolytic profile in the pigeon conflict model [90]. This may reflect species differences in the 5-HT$_{1C}$ receptor, or in the metabolism and disposition of ketanserin.

Another rat model claimed to be relevant to anxiety is the response to electrical stimulation of the periaqueductal gray (PAG). In humans this elicits unpleasant and fearful sensations [121] and in animals causes vigorous flight or defense reactions [122]. In this model mCPP acts as an anti-aversive agent; 5-HT$_2$/5-HT$_{1C}$ antagonists mianserin, cyproheptadine and ritanserin as pro-aversive agents; and selective 5-HT$_2$ antagonists ketanserin, pirenperone and spiperone as anti-aversive agents [123]. Since mCPP is clearly anxiogenic both clinically and in other animal models the relevance of this paradigm is uncertain, but it may apply to a particular type of anxiety. Recently Beckett et al. [124] have reported mCPP to be pro-aversive when the PAG was chemically stimulated by homocysteic acid. This effect was blocked by mianserin.

The difference between these results and those obtained using electrical stimulation of the PAG may be due to the stimulation of fibres of passage by the latter technique.

Taken as a whole these results suggest that 5-HT$_{1C}$ antagonists are anxiolytic in at least some animal models. This is consistent with reports of the clinical anxiolytic properties of mianserin [125–128] and the effectiveness of ritanserin in generalised anxiety disorder [129–131]. Metergoline, however, is not anxiolytic [75] and may be anxiogenic clinically [132]. This may reflect its non-specificity for 5-HT$_1$ subtypes [16] and possibly the different distribution of receptors in man and rat. It is of considerable interest that selective 5-HT$_{1C}$ receptor antagonists have been claimed to possess anxiolytic activity, being active in the SI and Geller-Seifter test, in a recent SmithKline Beecham patent [500].

Panic Disorder

The administration of mCPP to normal volunteers evoked anxiety resembling panic attacks in some subjects [84,85]. In panic disorder patients, mCPP was found to induce panic attacks in roughly half of those treated. These were reportedly indistinguishable from those normally experienced [81,85,133–135]. The increase in anxiety and panic reported by these patients was also greater than that of healthy volunteers [85,133,134] although this did not reach significance in the study by Charney et al. [81]. However this group may have achieved a supramaximal response.

Neuroendocrine responses to mCPP in panic disorder patients followed a similar pattern. Thus Kahn et al. found that plasma cortisol responses to mCPP were enhanced [133], as were ACTH and prolactin in female, but not male panic disorder patients [136]. However cortisol, prolactin and growth hormone responses were not different from healthy volunteers in the study of Charney et al. [81] as observed for the anxiety response.

The above evidence has been used to argue the existence of hypersensitive 5-HT receptors in panic disorder. Since the anxiogenic effects of mCPP are probably 5-HT$_{1C}$ receptor mediated (see above) these may be the hypersensitive 5-HT receptors in panic disorder. However the enhanced responses to mCPP could instead be secondary to hypersensitive anxiety mechanisms distal to 5-HT$_{1C}$ receptors themselves. This view is supported by the ability of caffeine [135,137,138], yohimbine [139] and lactate [140], anxiogenic agents with differing modes of action to mCPP, to also induce a greater degree of anxiety in panic disorder patients, although not all induce robust increases in cortisol or prolactin [135]. The hypothesis may be further supported by the lack of clinical efficacy of the 5-HT$_{1C}$ and 5-HT$_2$ receptor antagonist ritanserin in panic disorder [141] although an earlier open trial of the drug did suggest some benefit [142]. Furthermore the efficacy of tricyclic antidepressants [76] and the specific 5-HT reuptake inhibitor fluoxetine [77,78] after chronic administration may be mediated by down regulation of 5-HT$_{1C}$ receptors (see section on depression).

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is characterised by obsessions (recurrent, intrusive thoughts) and compulsions (repetitive behaviours) such as ritualistic washing or checking which the patient recognises as senseless. The patients experience significant anxiety but the most common complication of primary OCD is depression [75]. OCD is refractory to benzodiazepine anxiolytics, despite reduced anxiety levels [74]. However chronic treatment with the antidepressant chlorimipramine (Geigy) [143,144] was found to ameliorate symptoms to a greater degree than other tricyclic and MAOI antidepressants [145]. Since chlorimipramine is a relatively selective 5-HT reuptake inhibitor [146] this suggested that a defective 5-HT

system might be involved, as did the effectiveness of treatment with the 5-HT precursor tryptophan [147] and the correlation of clinical efficacy of chlorimipramine with reduced CSF 5-hydroxyindoleacetic acid levels, but not plasma levels, of the drug [148]. Subsequently, chronic treatment with specific 5-HT reuptake inhibitors such as fluoxetine, zimeldine (Astra), sertraline (Pfizer) and fluvoxamine (Duphar) were also found to be effective anti-obsessional treatments [149,150] while the 5-HT releaser fenfluramine (Servier) can augment the therapeutic action of chlorimipramine [151]. Unfortunately, none of the treatments are effective in more than 50% of the patients and this is only reached after approximately 6 weeks treatment [145,149]. MAOIs, which acutely enhance extraneuronal 5-HT, are also clinically effective in OCD [145] although not in all studies [143]. But noradrenergic reuptake inhibitors are not effective[145].

The administration of mCPP orally to OCD patients provoked anxiety and this response was greater than in healthy volunteers [152]. The drug also exacerbated obsessive compulsive symptoms [96,152–154] which in some cases had been absent for several months, although this did not occur in the study of Charney *et al.* [155] in which intravenous administration was used. None of the studies reported the induction of panic attacks in OCD patients. The effect of mCPP on OCD symptoms was antagonised by metergoline [75,96] which is a non-specific 5-HT$_1$/5-HT$_2$ receptor antagonist [16]. Since mCPP and metergoline act as agonist and antagonist respectively at 5-HT$_{1C}$ receptors, these findings may suggest that the receptors are in some way hypersensitive in OCD patients. Chronic administration of specific 5-HT reuptake inhibitors such as fluoxetine or MAOIs might therefore act by down-regulating these receptors, as suggested by evidence outlined in the section on depression and by the ability of chronic administration of fluoxetine and chlorimipramine to desensitise the behavioural effects of mCPP in OCD patients [157,158]. However not all evidence supports this hypothesis. Obsessive compulsive symptomology was not induced by MK 212 [156], an agonist at 5-HT$_{1C}$ receptors [61] with roughly fifty-fold selectivity over 5-HT$_2$ receptors [16]. This may reflect the drug's poor selectivity over 5-HT$_{1A}$ receptors [16] or its even higher affinity for the 5-HT$_3$ receptor (Table 3, [159]). Its affinity for many other sites is unknown and could also influence its effects on OCD patients, although in rats the stimulus cue of MK 212 generalized to mCPP and was blocked by metergoline and methysergide but not by specific 5-HT$_2$ receptor antagonists [160]. Another difficulty for the 5-HT$_{1C}$ hypothesis of OCD is the failure of acute fenfluramine, the 5-HT releaser, to induce OCD symptomology in OCD patients [154,161]. Although this type of drug might be expected to stimulate many 5-HT receptor subtypes simultaneously, which could account for this finding, it too produces a stimulus in rats which generalizes to mCPP [160] and induces anxiety in rats by 5-HT$_{1C}$ receptor stimulation [162]. It also has reasonable affinity for the 5-HT$_{1C}$ receptor itself [163].

Evidence from neuroendocrine responses to mCPP is also inconsistent with 5-HT$_{1C}$ receptor hypersensitivity in OCD. Patients had reduced cortisol responses to mCPP [152,156] and reduced prolactin responses in some [154,155,158] but not in all [152,154] studies. Responses of both hormones to MK 212 were also blunted [156]. Furthermore, although chronic fluoxetine [157] and chlorimipramine [158] abolished the ability of mCPP to increase obsessive and compulsive symptoms and anxiety, cortisol and prolactin responses were potentiated in the fluoxetine study [156], although increased plasma levels of mCPP could have been responsible [153]. Neuroendocrine evidence, therefore, suggests that 5-HT$_{1C}$ receptors may be subsensitive in OCD in direct contrast to the behavioural data.

These apparent contradictions may be explained if the involvement of 5-HT$_{1C}$ receptors in OCD symptomology resides in specific brain regions or if the hormonal responses to mCPP are not 5-HT$_{1C}$ receptor mediated. The latter possibility seems unlikely, as clinically mCPP-

induced cortisol and prolactin secretion are blocked by metergoline [87,97] and the relatively selective 5-HT$_2$/5-HT$_{1C}$ receptor antagonist ritanserin [83], although methysergide only blocked the prolactin response [97]. A third possibility is that a functional supersensitivity, which is either proximal or distal to the 5-HT$_{1C}$ receptors, underlies OCD and that the receptors themselves are down regulated by compensatory mechanisms.

Table 4: Pharmacology of trifluoromethylphenylpiperazine (TFMPP), MK 212, Quipazine, 2,5-dimethoxy-4-iodoamphetamine (DOI) and (–)2,5-demethoxy-4-iodoamphetamine (–)(DOM); agonists at 5-HT$_{1C}$ receptors

Receptor		5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1C}$	5-HT$_{1D}$	5-HT$_{1D\alpha}$	5-HT$_{1D\beta}$	5-HT$_{1E}$	5-HT$_2$	5-HT$_3$
Drug	Parameter									
TFMPP	pK$_D$	6.5	6.9	7.3	6.6	7.1^g	6.9^g	5.2^h	6.6^a	
	pEC$_{50}$	6.7	6.9	6.8	5.8				6.1^b	
	Efficacy	67.1	74.3	59.2	54.2			>50^k	Ant^b	
MK212	pK$_D$	5.3^c	5.0^c	6.2^c	>5.0^f				4.8^c	7.5^i
	pDC$_{50}$			6.1^b					4.7^b	
	Efficacy			90^b					80^b	
Quipazine	pK$_D$	5.5	6.5	6.7	5.9				6.2	8.5
	pEC$_{50}$	5.2	6.2	6.2	5.7				5.0	
	Efficacy	Ant	Ant	63	Ant				80	Ant
DOI	pK$_D$	4.7^j		7.8^d	5.6^j			5.5^h	7.5^j	
	pEC$_{50}$			7.0^d						
	Efficacy			58^d						
(–)DOM	pK$_D$			6.8^c						
	pEC$_{50}$			6.1^c						
	Efficacy			85^c						

Values for pEC$_{50}$ and efficacy (E$_{max}$ as a percentage of that for 5-HT) for agonist activity, pK$_B$ for antagonist efficacy and pK$_D$ from receptor binding studies are given. The functional assay for 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1D}$ receptor was inhibition of forskolin-stimulated adenylate cyclase activity. The assay for 5-HT$_{1C}$ and 5-HT$_2$ receptor function was stimulation of basal inositol phosphate accumulation in choroid plexus and cortical tissue, respectively. All data taken from [62] except:

^{a} [16] ^{b} [61] ^{c} [424]
^{d} [26] ^{e} [64] ^{f} G Price; personal communication
^{g} [69] ^{h} [425] ^{i} [159] (pIC$_{50}$) ^{j} [432] ^{k} [AM Brown, Personal communication]

The effect of mCPP on OCD symptoms, unlike its actions in panic disorder (see above), is not typical of other anxiogenic drugs. Thus yohimbine [164], lactate [165] and caffeine [166] cannot induce or exacerbate obsessive compulsive symptomatology, suggesting the existence of a specific dysfunction. Interestingly, these symptoms are not induced in healthy volunteers. While the evidence points to this dysfunction possibly involving 5-HT$_{1C}$ receptors, there is less evidence that an antagonist of these receptors would be of therapeutic benefit. Metergoline, the only 5-HT$_{1C}$ receptor antagonist studied to date, was found to modestly reduce obsessive compulsive symptoms in one study [75] but not in a second [96]. The lack of effect of metergoline could reflect the drug's lack of speficity for 5-HT$_{1C}$ receptors [16] (Table 1); indeed, in some clinical studies it was itself anxiogenic [132] and in one study it reversed the therapeutic action of chlorimipiramine, increasing anxiety and OCD symptomatology [167]. One possible property of metergoline that would be more prevalent in humans than in rodents is its agonist activity at 5-HT$_{1D}$ receptors [168], the effects of which are, as yet, unknown. If 5-HT$_{1D}$ receptor stimulation can induce OCD symptomatology, as has been suggested by Zohar & Kindler [169], this might underlie the action of mCPP which has agonist properties at 5-HT$_{1D}$ receptors and relatively high affinity for the 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ cloned human

receptors (Table 2). It might also be consistent with the failure of MK 212 to precipitate OCD symptomatology [156] as this drug has low affinity for the 5-HT$_{1D}$ receptor (Table 3), although its affinity for human 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptors is unknown. However the effects of metergoline on OCD symptomatology are inconsistent (as outlined above) and yohimbine, another 5-HT$_{1D}$ partial agonist [168], had no effect [164].

Another possibility is that metergoline could be a 5-HT$_{1C}$ agonist at the human receptor. Alternatively the effects of 5-HT reuptake inhibitors and MAOIs could be caused by effects on sites other than the 5-HT$_{1C}$ receptor.

Drugs of abuse

Alcoholism

Alcoholism is estimated to have a lifetime occurrence of 11-16% of the American population [170], and 5-HT has long been thought to influence this condition. Low cerebral spinal fluid (CSF) levels of the principal metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), have been observed in alcoholics [171,172]. This would seem to be trait-dependent as they were also observed in abstinent alcoholics [171] or in those suffering from withdrawal symptoms after one week of abstinence [173]. Banki [174,175] reported a negative correlation between 5-HIAA levels and number of days of abstinence.

Animal studies have provided further evidence. Levels of 5-HT and 5-HIAA were found to be reduced in some brain regions of alcohol-preferring rats [176]. Acutely, alcohol increases 5-HT release [177] and metabolism [178,179] in the striatum and increases 5-HIAA levels in several other brain regions including the nucleus accumbens [176] while reduced 5-HT turnover has been observed after chronic treatment [180]. Low 5-HT function has therefore been proposed to promote alcohol consumption. Treatments which increase serotonergic function might thus be expected to reduce alcohol consumption, and this has indeed been reported. Administration of the 5-HT precursors tryptophan [181] or 5-hydroxytryptophan (5-HTP) [176], the 5-HT releasing agent fenfluramine [176] and the 5-HT reuptake inhibitors fluoxetine [182–184] and sertraline [185], all reduce alcohol consumption when given acutely to rats. Intra-nucleus accumbens 5-HT has a similar effect [186]. The 5-HT$_{1A}$ agonist 8-OH-DPAT [176,187,188], 5-HT$_2$ and 5-HT$_{1C}$ agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) (Table 3, [176]) and 5-HT$_{1B}$ and 5-HT$_{1C}$ agonist 1-(3-(trifluoromethyl)phenyl)piperazine (TFMPP) (Table 3, [176]) also reduce consumption. Conversely, treatments that reduce 5-HT function, such as the 5-HT depletor para-chlorophenylalanine (PCPA) [189,190], enhance consumption. However the non-specific 5-HT$_1$ and 5-HT$_2$ receptor antagonists methysergide and metergoline [191,192] had no effect, while the 5-HT neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) had inconsistent effects [193,194].

Clinical trials are in agreement with results from animal models. In particular the 5-HT reuptake inhibitors fluoxetine, zimelidine, and citalopram (Lundbeck) all reduced the mean daily alcohol consumption of moderate alcoholics. The magnitude of this effect while consistently observed was only 9-17% [195–197]. Interestingly, the effect had a rapid onset, unlike the antidepressant actions of these drugs. This suggests mediation by increased synaptic cleft 5-HT levels. The 5-HT$_{1A}$ receptor agonist buspirone (Bristol-Myers Squibb) has also been shown to have modest clinical efficacy [198–200]. This could be mediated either by stimulation of postsynaptic 5-HT$_{1A}$ receptors, by desensitisation of cell body autoreceptors and hence enhanced 5-HT release [201], or acutely by stimulating these autoreceptors and hence decreasing 5-HT release.

In view of the above evidence that enhanced 5-HT suppresses ethanol intake, the effects of mCPP on alcoholics are surprising. The drug was reported to induce an alcohol-like 'high' feeling in alcohol abstaining alcoholics and, in a third of the subjects, induced a craving to drink alcohol [202]. One explanation for these results, proposed by Sellers et al. [203], is that mCPP can induce an ethanol-like stimulus. This is supported by the reported similarity between the ethanol cue in a rat drug discrimination paradigm and that of TFMPP [204], a 5-HT$_{1C}$/5-HT$_{1B}$ agonist resembling mCPP both pharmacologically (Table 3) and behaviourally in rats [59,60,88,205]. The perception of an alcohol-like stimulus in the absence of the full pharmacological effect may therefore cause craving.

An alternative explanation is that alcoholism is related to obsessive compulsive disorder [206]. Like alcoholism, OCD can be characterised by low 5-HT function [144,147], is ameliorated by specific 5-HT reuptake inhibitors (albeit after chronic administration [149]) and can be precipitated by mCPP (see above). It has also been suggested that the craving response to mCPP is secondary to the induction of anxiety [203], since alcoholism often coexists with anxiety [207]. This seems the least likely explanation, as anxiety induction was not noted in the Benkelfat et al. [202] study. However, the clinical efficacy of buspirone might be secondary to anxiolysis [208].

The pharmacology of mCPP (Table 2) suggests that 5-HT$_{1C}$ receptors may account for these actions. Recent reports that the 5-HT$_{1C}$ and 5-HT$_2$ antagonist (Table 1) ritanserin can reduce alcohol preference in rats [209] are possibly consistent with this. The effect was accompanied by increased water intake. It was not mediated by alcohol aversion nor by altered alcohol metabolism, and was not associated with body weight changes [209]. It may therefore specifically affect addictive mechanisms. Although this study reported effects at low doses, which might not be expected to block 5-HT$_{1C}$ receptors in vivo [66], only high 5-HT$_{1C}$ receptor blocking doses [66] were effective in a second model [210]. Ritanserin was also found to markedly reduce the alcohol intake of a small group of chronic alcoholics [211]. These patients reported that they had little difficulty in containing their consumption even after two weeks withdrawal from the drug. Mediation of these effects by 5-HT$_2$ receptor blockade seems unlikely: firstly mCPP is a 5-HT$_2$ receptor antagonist (Table 2), and secondly the specific 5-HT$_2$ receptor antagonist ketanserin (0.4 mg/kg po one hour pretest) did not affect rat alcohol preference in a recent study [210]. The reported ability of DOI and TFMPP, agonists at 5-HT$_{1C}$ receptors, to reduce alcohol consumption in rat models [176] may be due to their anorexic [205,212], sedative [59,213] or, in the case of DOI, hallucinogenic [214] actions. These effects were not reported in the clinical study of Benkelfat et al. [202]. The predominance of the craving response to mCPP in alcoholics may suggest hypersensitive 'craving' mechanisms.

In conclusion, the opposing effects of mCPP and ritanserin, both clinically and in animal models, must be considered evidence of possible 5-HT$_{1C}$ involvement. Further evidence must await the development and testing of more selective compounds. Indeed the effects of mCPP and ritanserin, while seemingly behaviourally specific and opposite, may be unrelated, as may be the case if ritanserin were acting as an anxiolytic (see above). The opposite nature of the effects of treatment which enhance 5-HT function such as 5-HT reuptake mechanisms (see above) and the mCPP/ritanserin studies, suggest the existence of several serotonergic mechanisms modulating alcoholism. When 5-HT function is enhanced at several receptor subtypes simultaneously the net result is alcohol intake inhibition. Conceivably this also occurs when 5-HT$_{1C}$ receptors are selectively blocked. Given the modest clinical efficacy of 5-HT reuptake inhibitors there is considerable scope for new forms of treatment.

Oth r drugs of abuse

In addition to its effects on alcohol abuse, ritanserin has been anecdotally noted to be of use in patients withdrawing from other drugs of abuse [214]. This has led to an examination of its actions in rat models of cocaine and opiate dependence. Ritanserin was found to reduce both cocaine and fentanyl (Janssen) preference of rats [216,217]. The magnitude of the effect on cocaine was less than that observed for alcohol but greater than that observed with fentanyl [217]. This probably reflects the degree of reinforcement engendered by the drugs. Ritanserin does not interact with the cues for cocaine or fentanyl [216,217] which argues against any direct effects of the drug. Since drugs of abuse are thought to induce reinforcing effects by activating the dopamine reward pathways of the nucleus accumbens [218], it is of interest that ritanserin does not affect intracranial self-stimulation [216,217] which is thought to act on the same system. Ritanserin may therefore have a specific action on a reinforcing pathway common to drugs of abuse and perhaps distal to dopaminergic mechanisms of the nucleus accumbens. Whether this is 5-HT$_{1C}$ or 5-HT$_2$ receptor mediated is not yet clear.

Depression

A large body of evidence suggests that the serotonergic system is defective in depression. Most neurochemical and neuroendocrine studies of depressive patients are consistent with the existence of a serotonergic deficit, while SSRIs and MAOIs are clinically effective antidepressants and both increase extraneuronal 5-HT acutely (for review, see [219]).

One argument in favour of 5-HT$_{1C}$ receptor involvement in depression is the clinical efficacy of three 5-HT$_2$/5-HT$_{1C}$ receptor antagonists: mianserin [125,126,128], cyproheptadine [220] and ritanserin [221-223]. However, none of these drugs has been reported to exert immediate therapeutic action [221,223]. This may argue against simple 5-HT$_{1C}$ receptor blockade as a mode of action. Alternatively it might reflect a property of the disease state.

Clinically, the effect of treatments expected to enhance 5-HT$_{1C}$ function is also unclear. Thus mCPP administration to healthy volunteers did not cause depressive symptoms in most studies [80,81,84,134,224-226], with one exception [86]. In addition it does not potentiate depression in depressive patients and neither cortisol nor prolactin responses in these patients differed from that of healthy volunteers [133,134,226]. Indeed when given subchronically it ameliorated depressive symptomatology in elderly depressives [227]. These findings argue against direct 5-HT$_{1C}$ involvement in depression. However antidepressants may exert their therapeutic efficacy after chronic administration through adaptive changes to the serotonergic system [228], and, in particular, to the 5-HT$_{1C}$ receptor, as suggested by studies in rats. These involve models of 5-HT$_{1C}$ receptor function and are summarised in Table 5. Chronic treatments with the MAOIs phenelzine (Parke-Davis) or nialamide (Pfizer) have been reported to desensitise mCPP-induced hypolocomotion [229], a putative 5-HT$_{1C}$ mediated behaviour (Table 3, [59]). The MAOI tranylcypromine (SmithKline Beecham) reduced mCPP-induced penile erections [230], another putative 5-HT$_{1C}$ mediated response (Table 3, [231]) after chronic treatment, while chronic clorgyline reduced mCPP-induced hypophagia [232] and hyperthermia [233]. Of these last two paradigms mCPP-induced hypophagia is relatively well characterised as 5-HT$_{1C}$ mediated (Table 3, [59,66]) while hyperthermia is likely to be 5-HT$_{1C}$ mediated (Table 3, [233]). The effects of selective 5-HT reuptake inhibitors have been less extensively studied. One such drug, chlorimipramine [181] reduced mCPP-induced hypothermia after chronic treatment [233] while both chronic sertraline and citalopram reduced mCPP induced hypolocomotion [234]. However, chronic ORG 6997 (Organon) did not affect the rat penile erection model [230]. Noradrenergic reuptake inhibitors do not appear to share these properties. Thus, although imipramine (Ciba-Geigy) [181] reduced hyperthermic

responses to mCPP [233], it potentiated mCPP-induced hypolocomotion [235] and prolactin release but did not affect corticosterone or growth hormone release [236]. Also another noradrenergic reuptake inhibitor, desipramine (Ciba-Geigy) [181], did not alter the hypolocomotor response [229]. The atypical antidepressant iprindole (Wyeth Research) was also without effect after chronic administration [229]. These findings might be caused by altered metabolism or disposition of mCPP, but they suggest that, in rats, treatments that enhance extraneuronal 5-HT levels desensitise 5-HT$_{1C}$ receptor function. This in turn may cause, or contribute to, their antidepressant efficacy. The therapeutic effect of subchronic mCPP [227] could therefore also be explained by 5-HT$_{1C}$ receptor desensitization. Indeed, chronic mCPP desensitises mCPP-induced hypolocomotion [237-239] and changes in cerebral glucose metabolism [238] without altering its pharmacokinetic profile [238,239]. Chronic imipramine treatment is reported to reduce the hyperthermic effects of mCPP in humans [157] and in rats [233].

Table 5: The effects of chronic antidepressant treatments on putative rat models of 5-HT$_{1C}$ receptor functional activity.

Treatment		Paradigm (mCPP-induced)	Effect	Reference
Class	Drug			
MAOI	Phenelzine	Hypolocomotion	Decrease	229
	Nialamide	Hypolocomotion	Decrease	229
	Tranylcypromine	Penile erections	Decrease	230
	Chlorgyline	Hypophagia	Decrease	232
		Hyperthermia	Decrease	233
SSRI	Chlorimipramine	Hyperthermia	Decrease	233
	Sertraline	Hypolocomotion	Decrease	234
	Citalopram	Hypolocomotion	Decrease	234
	ORG 6997	Penile erections	-	230
SNRI	Imipramine	Hyperthermia	Decrease	233
	Desipramine	Hypolocomotion	Increase	235
		Hypolocomotion		229
Atypical	Iprindole	Hypolocomotion		229

MAOI: monoamine oxidase inhibitor
SNRI: selective noradrenergic reuptake inhibitor
SSRI: selective serotonin (5-HT) reuptake inhibitor
Atypical: atypical antidepressant

This may suggest that 5-HT$_{1C}$ receptors can be desensitised by this drug or that body temperature is affected by some other mechanism. Whether all these results can be safely interpreted as evidence of 5-HT$_{1C}$ receptor desensitization awaits studies of 5-HT$_{1C}$ receptor binding and PI hydrolysis.

Finally, the specific 5-HT reuptake inhibitor fluoxetine (a racemic mixture) and its (-) isomer have been shown to have some affinity for the 5-HT$_{1C}$ site [240]. Since this is roughly ten-fold less than their affinities for the 5-HT reuptake site it may not explain their antidepressant efficacy. Fluoxetine is metabolised to the long-acting metabolite norfluoxetine. This too has

been found to bind to 5-HT$_{1C}$ receptors, and a patent for its use in feeding disorders, OCD, alcoholism, sleep disorders and migraine has been published [502].

In conclusion, the evidence for a role for 5-HT$_{1C}$ receptors in depressive illness is at present neither wholly consistent nor complete. The therapeutic benefit of ritanserin (and presumably mianserin and cyproheptadine) may be secondary to improved sleep, anti-anxiety and energy restoring properties. Some of these at least may not be 5-HT$_{1C}$ mediated.

Migraine

When mCPP was administered to bulimic patients, migraine-like headaches were reported eight to twelve hours later [241]. This response was correlated with plasma levels of mCPP and was more pronounced in patients with a personal or family history of migraine, an effect confirmed in a recent study of migraine patients [242]. Migraine patients given mCPP had enhanced cortisol and temperature responses [242]. Fozard & Gray [243] have argued that 5-HT$_{1C}$ receptor stimulation might be an important step in the pathogenesis of migraine for two reasons: firstly, mCPP activates 5-HT$_{1C}$ but antagonizes 5-HT$_2$ receptors (see mCPP section). and secondly, methysergide pizotifen, mianserin and cyproheptadine, all of which are non-specific 5-HT$_{1C}$ and 5-HT$_2$ receptor antagonists are clinically effective antimigraine agents, but the selective 5-HT$_2$ antagonist [16] ketanserin is not [244]. Recently Brown et al. [63] have demonstrated that two effective antimigraine agents, ergotamine (Wellcome) and dihydroergotamine (Sandoz), are also potent 5-HT$_{1C}$ agonists but only occasionally induce headaches [245]. However, this may be due to the additional potent 5-HT$_1$-like constrictor activity of these drugs on large dilated cerebral arteries [63], which may confer antimigraine efficacy [245], this action is shared by sumatriptan (Glaxo), a novel antimigraine agent [246]. Since both drugs also activate other receptors (e.g. α adrenoceptors and dopamine receptors) these could conceivably mediate their effects [247]. It could also be argued that the α_1 adrenoceptor blocking activity of ketanserin (Table 1) prevented antimigraine efficacy. The relationship of 5-HT$_{1C}$ receptors to the clinical efficacy of the 5-HT$_{1C}$/5-HT$_2$ receptor antagonists may also be disputed since they too have additional actions. Thus cyproheptadine and pizotifen have similar and appreciable affinities for dopamine, muscarinic cholinergic and α_1 adrenoceptor sites, and lower affinities for α_2 adrenoceptors (Table 1). They also have an affinity for histamine H$_1$ receptors equal to that for 5-HT$_2$ and 5-HT$_{1C}$ sites (Table 1, [15]). Mianserin, too, has affinity for histamine H$_1$ receptors and lower affinity for both α_1 and α_2 adrenoceptors, but has low affinity for dopamine receptors and is inactive at cholinergic receptors (Table 1, [15]). Methysergide, however, has little affinity for histamine, α adrenoceptors or cholinergic receptors (Table 1, [15]). These four drugs, therefore, only share high affinity at the 5-HT$_2$ and 5-HT$_{1C}$ sites, and the lack of clinical efficacy of histamine H$_1$, cholinergic, dopaminergic or α adrenoceptor antagonists [248] suggests that 5-HT$_{1C}$/5-HT$_2$ receptors alone are clinically relevant. The modest antimigraine efficacy of ICI 169,369 [249], another relatively specific 5-HT$_2$ and 5-HT$_{1C}$ receptor antagonist [100,250], may be attributable to the dose used, while the clinical efficacy of chronic administration of 5-HT reuptake inhibitors such as amitriptyline (Merck Sharp & Dohme) [251] and fluoxetine [252,253] as migraine prophylactics may be caused by down-regulation of 5-HT$_{1C}$ receptors (see section on depression and Table 5).

One interesting observation of the migraine-precipitant action of mCPP is the long time interval between administration and headache; peak mCPP concentrations were seen two to three hours after administration [241,242], whereas headache occurred up to twelve hours later.

This suggests an indirect mode of action and may be consistent with the prophylactic but not acute efficacy of 5-HT$_{1C}$/5-HT$_2$ receptor antagonists in migraine [243].

In conclusion, 5-HT$_{1C}$ receptors may be involved in migraine. Further proof awaits the development of more specific compounds and further testing of existing drugs.

Sleep Disorders

In man, the serotonergic system has been considered hypnogenic. Treatments that enhance 5-HT function, such as the administration of the 5-HT precursors tryptophan [254,255,256] or 5-hydroxytryptophan (5-HTP) [256,257], increase either sleep time, the duration of slow wave sleep (SWS) or the duration of rapid eye movement sleep (REMS). Conversely the 5-HT depleter PCPA reduces REMS [258]. In cats, PCPA or 5-HT neurotoxic lesions can lead to total insomnia that can be reversed by 5-HTP [256]. As with many other functions of 5-HT, the recognition of 5-HT receptor subtypes has suggested that 5-HT may have differing effects on sleep depending on which subtype is studied. 5-HT$_{1A}$ receptor agonists, for instance, increase wakefulness in both rats [259,260] and humans [261].

MCPP reduced total sleep time, sleep efficiency, SWS and REMS in two clinical studies [262,263]. Wakefulness was increased and subjective behavioural effects of mCPP seemed more prominent than in patients given mCPP during waking hours [262]. This may reflect the absence of environmental distraction. The effects of mCPP are consistent with reports that the 5-HT reuptake inhibitors zimelidine and indalpine (Groupe Pharmuka) also reduce total sleep time and REMS when given acutely [264]. In rats the mixed 5-HT$_2$/5-HT$_{1C}$ agonist 2,5-dimethoxy-4-methylamphetamine (DOM) (Table 3) reduced both SWS and REMS [265]. The effects of the 5-HT reuptake inhibitor zimeldine are more complex. Initially it is reported to increase wakefulness and reduce REMS but after roughly two hours it enhances SWS [266]. Other 5-HT reuptake inhibitors, such as fluoxetine [267], indalpine [268] and alaproclate (Astra) [269], also reduce REMS and can enhance SWS [267,270]. The biphasic effects of this class of compounds is likely to reflect the stimulation of different 5-HT receptor subtypes by the released 5-HT. The increased wakefulness is unlikely to be 5-HT$_2$ or 5-HT$_{1C}$ receptor mediated as it is not blocked by ritanserin [266]. Curiously, TFMPP given to rats reduced REMS but also increased SWS in the second hour after administration, although this effect was not dose-dependent [267]. The drug's profile of action was thus dissimilar to that of mCPP in humans but similar to 5-HT reuptake inhibitor; its action may therefore be due to 5-HT releasing properties [71].

The effect of drugs with 5-HT$_{1C}$ antagonist properties is clearer. The 5-HT$_2$ and 5-HT$_{1C}$ receptor antagonist, ritanserin, increases SWS, reduces sleep onset latency and improves subjective sleep quality in both young [272-274] and old [275] healthy volunteers. REMS is reduced in some [272,276] but not all [275,277] reports. A shift from early stage SWS to later, deeper SWS stages is generally reported [272,273,275-277]. Ritanserin has also proved efficacious in insomniac patients [278] and patients suffering from dysthymia (depressive neurosis) [277]. The drug achieved these effects acutely [273,275,276,279], chronically [273,275,277] and dose-dependently [276]. Only Adam & Oswald [275] reported withdrawal wakefulness. Other drugs with 5-HT$_{1C}$ antagonist actions such as mianserin [280], cyproheptadine [281,282] and pizotifen [283] have similar effects, but methysergide [284] and metergoline [282] do not. This may reflect the lack of specificity of these compounds (Table 1, [16]) such as their 5-HT$_{1D}$ partial agonist actions [168]. In rats, too, ritanserin increases SWS [265,266,285] although not always significantly [18]. However, some studies suggest that the deepest phase of SWS (SWS2) is increased but total SWS is not [266,285] and not all report

significantly reduced wakefulness [18,266]. As in clinical studies, REMS was reduced [18,265,285] although not universely [266]. Only one study of the effects of two other 5-HT$_2$/5-HT$_{1C}$ receptor antagonists with an otherwise relatively clean profile of action, ICI 169,369 [250] and ICI 170,809 (Table 1), has been published. However while they increased REMS latency, as did ritanserin, ICI 169,369 had no effect and ICI 170,809 had little effect on SWS, although in the same study ritanserin reduced it [286]. Unfortunately SWS in this study was not subdivided into SWS1 and SWS2. Thus both antagonists might have increased SWS2 as seen by others. The effect of ritanserin on all sleep stages can be reversed by the 5-HT$_{1C}$/5-HT$_2$ agonist DOM [287]. Recently the effect on rat sleep patterns of SR 46349B, a relatively selective 5-HT$_2$ receptor antagonist (Table 1) was studied. This drug also reduced REMS and increased REMS latency, as did ritanserin [18]. This suggests that 5-HT$_2$ receptor antagonism mediates this effect. As neither SR 46349B nor ritanserin clearly affected SWS or wakefulness in this study it is not possible to decide whether these functions are 5-HT$_2$ or 5-HT$_{1C}$ receptor mediated [18].

The shift in sleep pattern derived from ritanserin and other 5-HT$_2$/5-HT$_{1C}$ receptor antagonists is subjectively reported to be beneficial and refreshing despite the reduced amount of REM sleep. The effects are also not associated with sedation [272]. Given the largely opposite effects of mCPP it seems possible that 5-HT$_{1C}$ receptors might mediate these actions. Should reduced REMS be caused by 5-HT$_2$ receptor blockade, as suggested by the results of Rinaldo-Carmona et al. [18], and should increased SWS and reduced wakefulness be 5-HT$_{1C}$ receptor mediated, then selective 5-HT$_{1C}$ antagonists could be of particular therapeutic use in the treatment of sleep disorders. Further trials with more selective drugs are awaited.

Feeding Disorders

Administration of mCPP and TFMPP to food-deprived [60,428,430] or freely feeding [205] rats reduces subsequent food, but in the case of mCPP, not water [288] intake. The effect is not secondary to anxiety as it is not reversed by benzodiazepine anxiolytics [88]. Nor is it likely to be secondary to hypolocomotion as, unlike hypophagia, the effect is not blocked by either cyanopindolol or (−)propranolol [60]. Also TFMPP administration into the hypothalamus causes hypophagia only [289]. Since the hypophagia was not blocked by the antiemetic trimethobenzamide, mCPP is unlikely to induce nausea [290]. The accelerated appearance of the postprandial satiety sequence following both mCPP and TFMPP suggests that a satiety mechanism is probably responsible for their hypophagic actions [Kitchener & Dourish, unpublished observations].

The action of mCPP was blocked by the non-selective 5-HT$_2$/5-HT$_{1C}$ receptor blockers metergoline, mianserin, mesulergine and 1-NP but not by the selective 5-HT$_2$ antagonist ketanserin or 5-HT$_3$ antagonist ICS 205,930 (Table 4, [60]). Inhibition of mCPP-induced hypophagia by ten antagonists was found to correlate only with their affinities for the 5-HT$_{1C}$ site [66]. Studies on the pharmacology of TFMPP-induced hypophagia have produced a less clear discrimination between the effects of 5-HT$_{1C}$ and selective 5-HT$_1$ receptor antagonists (Table 3, [430]). MK 212 also reduces feeding in rats [291] but the mechanism of action is unknown. The hypophagic effects of DOI [292] and quipazine (Miles Scientific) [293], both of which have high affinity for the 5-HT$_{1C}$ site [16,26], have been reported to be mediated by 5-HT$_2$ receptors because they are ketanserin sensitive.

This may reflect differences in experimental design but is most likely to be secondary to response competition between feeding and the behavioural effects of 5-HT$_2$ receptor

stimulation, one possibility being hallucination [214]. Indeed DOI, at least, disrupts the postprandial satiety sequence [294] while quipazine reduces water intake also [288].

The effects of $5\text{-HT}_1/5\text{-HT}_{1C}$ antagonists have also implicated 5-HT_{1C} receptors in the control of food intake. Mianserin, cyproheptadine and 1-NP all increased the food intake of freely feeding rats over four hours as did mesulergine, albeit not significantly [60]. Likewise Dourish et al. [295] observed increased food intake after administration of metergoline, methysergide, mianserin and methiothepin. Metergoline, ritanserin and methysergide increased the consumption of palatable wet mash in rats partially sated prior to drug injection [296]. In contrast, the specific 5-HT_2 antagonist ketanserin had no effect on food intake in freely feeding rats [59,295]; neither did ritanserin at low doses [295,297] which may not block 5-HT_{1C} receptors [66]. Increased food intake is only seen under conditions of satiety where low rates of feeding occur. Under conditions of high feeding rates none of these drugs was effective [60,296]. This is consistent with mediation by blockade of satiety signals and may explain the contradictory findings of cyproheptadine's hyperphagic actions [298,299]. It is also of interest that the hyperphagic effects of these compounds has only rarely been observed to increase daily food intake or body weight [60,295,300-302], the exceptions being metergoline [295] and high doses of ritanserin [297]. This may suggest the presence of compensatory mechanisms.

In healthy volunteers or bulimics, mCPP has not been reported to affect appetite [303] possibly due to the short nature of most studies which are not designed to elicit changes in appetite. Since mCPP-induced anxiety is seen at doses ten-fold less than those necessary for hypophagia in rats [60,205], the doses used clinically may have been too low. However fenfluramine, a drug that enhances synaptic cleft 5-HT, is a noted, clinically effective anorexic agent [304]. It has been claimed to act via 5-HT_2 receptors in rats as it was blocked by ketanserin [305], but this was not confirmed by Neil & Cooper [288]. This group concluded that fenfluramine anorexia was 5-HT_1, but not 5-HT_{1A} or 5-HT_{1B}, mediated. However they could not block the effects of fenfluramine with the non-specific $5\text{-HT}_2/5\text{-HT}_{1C}$ receptor antagonist ICI 169,369 (Table 1, [17,100,250]) and only achieved a modest non-significant antagonism with mianserin. Consistent with these results were those of Garattini et al. [306], which showed antagonism of fenfluramine by metergoline but not by doses of ritanserin that might be specific for 5-HT_2 receptors [66]. However, a firm attribution of fenfluramine's actions (or at least a component of them) to 5-HT_{1C} receptor stimulation is not possible at present, although the drug has considerable affinity for the 5-HT_{1C} receptor [163] and has been reported to cause anorexia in rats pretreated with the 5-HT synthesis inhibitor p-chlorophenylalanine [307]. This suggests that the drug may act directly on postsynaptic 5-HT_{1C} receptors.

A second class of drugs that increase synaptic cleft 5-HT, the specific 5-HT reuptake inhibitors, are also clinically effective anorexic agents [308,309]. Fluoxetine [310-312], paroxetine (SmithKline Beecham) [309], zimelidine (Astra) [313], RU 25591 (Roussel UCLAF) [314] and sertraline [315,316] are hypophagic in rodents. Like fenfluramine the mode of action of these drugs is uncertain. Although the effect of sertraline was blocked by metergoline and methysergide, but not ketanserin [315], fluoxetine was not blocked by metergoline or LY 53857 [317], both of which are non-specific antagonists of 5-HT_{1C} receptors (Table 1). The effect of drugs which enhance extraneuronal 5-HT may be mediated via more than one 5-HT receptor subtype. Thus 5-HT can reduce food intake when injected into the paraventricular nucleus of the hypothalamus [318] or when given peripherally [319]. Both 5-HT_{1B} and 5-HT_{1C} receptors may mediate central hypophagic mechanisms [60,289], while 5-HT_2 receptors may mediate them peripherally [297,319,320]. The above evidence shows that the hypophagic actions of treatments which may enhance 5-HT_{1C} receptor function

are not well characterised in species other than rodents. Clinically effective anorectic agents may therefore attain their efficacy via mechanisms other than 5-HT$_{1C}$ receptor stimulation.

Obesity

The hypophagic effects of 5-HT$_{1C}$ receptor stimulation might be applied as an aid to weight loss, particularly where obesity is life threatening, as in those with cardiovascular disease. The 5-HT reuptake inhibitor fluoxetine has been shown to induce weight loss in obese patients [321-323] albeit not of great magnitude. Fenfluramine has long been recognised as an effective anorexic agent [304]. This drug achieves its anorexic response rapidly to give a new body weight set point which is often lost on withdrawal. Since the drug can induce 5-HT lesions [304], albeit at high doses, alternative therapies might well be more acceptable.

Bulimia Nervosa

Another possible indication is Bulimia Nervosa. This disorder is estimated to affect 1.3-10.1% of American women [79] and is characterised by compulsive eating binges followed by self-induced vomiting, laxative abuse, or other methods to prevent weight gain. It can cause serious morbidity and even mortality. Fenfluramine has been claimed to have beneficial effects in bulimics, reducing bingeing [324] in one acute study. A second study observed reduced bingeing within a week of chronic fenfluramine administration [325]. In both studies fenfluramine may have acted by a direct reduction of feeding behaviour, as Blouin et al. [325] reported a reduction in caloric intake in the fenfluramine treated patients. Antidepressants represent a second class of treatment. Thus monoamine oxidase inhibitors such as phenelzine [326] and isocarboxazid (Roche) [327], which would be expected to increase extraneuronal 5-HT levels, are clinically effective. The specific 5-HT reuptake inhibitor fluoxetine is also effective [79,328]. Interestingly so is trazodone [329], which could act via its metabolism to mCPP [56]. The onset of fluoxetine's therapeutic effects is rapid [79] suggesting that, as with fenfluramine, appetite suppression may be involved. This is consistent with the reported relapse of two fluoxetine treated patients when given the 5-HT$_{1C}$/5-HT$_2$ receptor antagonist cyproheptadine [330]. However the noradrenergic reuptake inhibitors [146] imipramine [331], desipramine [332] and nomifensine (Hoechst) [333] are also effective, which could reflect the considerable overlap between depression and bulimia [328]. One antidepressant that was not effective in the treatment of bulimia was mianserin [334]. Since blockade of 5-HT$_{1C}$ receptors by this drug [16] may enhance appetite (see above and the following section) this may not be surprising. However, chronic administration of antidepressants that enhance extraneuronal 5-HT may down-regulate 5-HT$_{1C}$ receptors (see section on depression and Table 5), which could detract from efficacy. The possibility remains that 5-HT$_{1C}$ receptor agonists might be of use in the treatment of Bulimia Nervosa.

Anorexia Nervosa

Clinically the non-specific 5-HT$_{1C}$/5-HT$_2$ antagonists cyproheptadine [301,302,335,336] and pizotifen [337,338] stimulate appetite. Both of these drugs also share a high affinity for histamine receptors (Table 1, [15]). However mianserin, methysergide and metergoline are not reported to increase weight [306,339]. These discrepancies might result from the non-specific nature of the drugs. The effect of the relatively specific 5-HT$_{1C}$/5-HT$_2$ receptor antagonist ritanserin might therefore be more relevant. Out of six large clinical trials with this drug, only one reported mild weight gain as a side effect [223] and this was tolerated after the first month. Another study [131] observed one case of increased appetite in twenty-two patients given 5 mg/kg daily for four weeks but other groups using higher [130,141,221] or similar doses [129] did not. No effects on appetite were reported in several smaller trials [272,275,279].

Furthermore, no alterations in appetite were observed in a study with ICI 169,369 on migraine [249]. One reason for the discrepancy between the effects of cyproheptadine and pizotifen and the studies of ritanserin may be that the latter were not set up to study appetite, which might thus have been overlooked. Alternatively the expected increase in appetite may be mild in most patients.

The above properties suggest that 5-HT_{1C} receptor antagonists might be of use in the treatment of anorexia nervosa. However, to date, no drug has consistently proved effective in this disorder. If appetite stimulation could improve the symptomology of anorexia one would predict that 5-HT_{1C} receptor antagonists or chronic treatment with antidepressants which enhance extraneural 5-HT might prove effective. Since neither the $5\text{-HT}_{1C}/5\text{-HT}_2$ receptor antagonist cyproheptadine [340,341,342] nor the 5-HT reuptake blocker chlorimipramine [343] had therapeutic value in anorexics, this seems unlikely.

5-HT_{1C} receptors and feeding disorders: Summary

In conclusion 5-HT_{1C} receptor stimulation is very likely to mediate hypophagia. This might suggest therapeutic utility in obesity and in the control of binge eating in bulimics. Unfortunately the anxiogenic properties of 5-HT_{1C} receptor agonists might prove a significant contraindication in the absence of any evidence that 5-HT_{1C} receptor subtypes exist that differentiate between the two actions. The possibility of tolerance to repeated administration of 5-HT_{1C} receptor agonists, as reported by Sills et al. [237], Freo et al. [238] and Ulrichsen et al. [239], might also be a problem. 5-HT_{1C} receptor blockade may produce increased appetite and weight gain. Drugs with these properties could therefore prove useful in the treatment of anorexia nervosa.

Cognition impairment

Although data on the role of 5-HT in learning and memory has been inconsistent, it is generally thought treatments that enhance 5-HT function led to impaired learning and memory [344]. It was therefore surprising when animal studies with 5-HT reuptake inhibitors such as alaproclate, zimeldine [345] and fluoxetine [346,347] observed cognitive enhancement after acute administration. Altman et al. [348], however, reported that the effects of alaproclate and zimeldine were opposed by pretreatment with quipazine, a 5-HT agonist, but not affected by cyproheptadine. They speculated that the effects of 5-HT reuptake inhibitors may be mediated by effects other than enhanced extraneuronal 5-HT [348].

Clinically, a number of studies have reported cognition-enhancing effects of reuptake inhibitors. Thus chronic citalopram (Lundbeck) improved concentration and absent-mindedness in demented patients [349] but this effect was not reproduced in a second larger study [350]. Chronic fluoxetine enhanced memory function in depressive patients in two studies [351,352] but not in a third [353]. However, as depression impairs cognition [351], these effects may be secondary to clinical improvement. Chronic zimeldine attenuated alcohol-induced memory impairment [354] and chronic fluvoxamine was reported to improve memory task performance in patients with alcohol amnesic disorder [355]. In healthy volunteers neither acute [356,357] nor subchronic fluvoxamine had any effect on learning and memory performance [358]. Chronic clomipramine enhanced verbal fluency, the ability to recognise nonsense words and motor function [359], while acute sertraline was considered to induce an 'alerting' response [360]. However in elderly volunteers subchronic fluvoxamine had little effect on psychomotor function [361] as did subchronic treatment with sertraline which, in addition, had no effect in memory tests [362]. The studies seem to suggest that clinically, chronic treatment with this class of drugs is more likely to produce enhanced cognition. This

may therefore be caused by the induction of neurochemical changes such as receptor down-regulation (see section on depression).

MCPP has been administered to Alzheimer's disease patients and produced an elevated anxiety response compared with normal age-matched volunteers at a higher [225] but not at a lower [224] dose. Cognition was also impaired to a greater extent at the higher dose [225] but only the lower dose of mCPP was found to worsen episodic memory of the elderly volunteers [224]. These effects could well be secondary to anxiety or light-headedness/dizziness [84,224,225]. MCPP-induced cortisol and prolactin release was not altered in Alzheimer patients after either low [224] or higher [225] doses.

Drugs with 5-HT$_{1C}$ receptor antagonist properties have been reported to enhance cognitive performance in some animal studies. Thus post-training mianserin, metergoline and methysergide improved memory of mice for an aversive behaviour [363]. Mianserin also attenuated age-induced deficits in passive avoidance retention of rats [264] and protected rats against an hypoxia-induced deficit [347]. These effects are probably 5-HT$_2$ mediated, as the selective 5-HT$_2$ receptor antagonist ketanserin [16] had similar effects in all three models [363,364,367].

Clinically, chronic mianserin tended to impair the performance of both psychomotor and memory tests [358,361,362]. This effect was thought to be secondary to the drug's sedative properties and was less pronounced after several days of treatment. Sedative properties are common to most of the older 5-HT$_{1C}$/5-HT$_2$ receptor antagonists due to their affinity for histamine H$_1$ receptors (Table 1) and was thought to account for the psychomotor retarding effects of acute cyproheptadine, although memory was unaffected in this study [365]. One other such drug, ritanserin, has been reported to enhance motivation and increase subjective energy levels [221]. At present, therefore, there is little evidence to support a role for 5-HT$_{1C}$ receptors in cognition.

Schizophrenia

MCPP has been reported to increase [366-368], have no effect [369], or decrease [370] psychotic symptomology. Blunted ACTH and prolactin responses to mCPP have been reported by Iqbal et al. [368] but were not seen in other studies [366,369,370], although Kahn et al. [370] reported blunted temperature responses to mCPP. Negative symptoms were unaltered by mCPP [366].

Conversely ritanserin has been reported to reduce negative/affective symptoms in schizophrenia (anergia, anxiety/depression, activity, hostility [221,371,372]), as has cyproheptadine [373]. Ritanserin is also reported to reduce neuroleptic-induced extrapyramidal side effects [374] and those induced by the dopamine precursor DOPA in patients with Parkinson's disease [375,376]. Furthermore it may prevent neuroleptic-induced akathesia [377]. These properties are shared by the atypical antipsychotic clozapine, on which basis it is considered to be superior to classical neuroleptic agents [378]. Since, like ritanserin, clozapine has high affinity for 5-HT$_2$ receptors (Table 6, [378]) and an even higher affinity for 5-HT$_{1C}$ sites (Table 6, [379]), these might mediate their actions. Indeed a high affinity for the 5-HT$_{1C}$ receptor is also possessed by several other putative atypical [380] antipsychotic agents including tiospirone (Mead Johnston) [379,380], fluperlapine (Sandoz) [380] and rilapine (Knoll Pharmaceuticals) [380]. However similar efficacy against negative symptoms and neuroleptic-induced extrapyramidal side effects has also been claimed for setoperone [381], risperidone [372] and melperone (Pharmacia) [382-384] while preclinical evidence suggests

that amperozide (Pharmacia) [385-387] is also atypical. All of these drugs have moderate or, in the case of amperozide and melperone, submicromolar affinities for the 5-HT_{1C} site [16,379,380]. Clearly no correlation can exist between 5-HT_{1C} receptor affinity and atypical antipsychotic properties. However, all the above compounds also have considerable affinity for the 5-HT_2 receptor [16,379,380] with tiosperone, rilapine, risperidone, setoperone, amperozide and melperone having between twenty- and one hundred and sixty-fold selectivity for the site [16,379,380], although tiosperone was not selective in the study of Canton et al. [379]. Hence 5-HT_2 receptor antagonism is much more likely to be the determinant of an atypical antipsychotic profile, although this does not account for the absence of such properties from chlorpromazine, spiperone and loxapine – all of which have high affinity for both 5-HT_2 and dopamine D_2 sites [380]. As 5-HT_{1C} receptors do not seem to be important in the action of antipsychotic drugs the induction of psychotic symptoms by mCPP is either secondary to anxiogenesis or mediated by properties unrelated to 5-HT_{1C} receptors. Such an effect may be observed by the drugs antagonist efficacy at 5-HT_2 receptors (Table 2).

Figure 3: Antipsychotic agents

Autism

Autistic disorder is a syndrome originating in early childhood. It affects two to five children in every million, and is characterised by prominent distortions in social, linguistic and cognitive development. Pervasive lack of interest in others, and unresponsiveness to them, are essential features of the disorder.

Autistic children who develop spoken language often exhibit abnormal speech patterns including senseless or compulsive repetition of words heard (echolalia). Motor stereotypes such as hand flapping are common, as are self-abusive behaviours like head banging. Resistance to change is also characteristic. In the 1960s the syndrome was often described as early schizophrenia.

One prominent feature of autism is the presence of elevated plasma levels of 5-HT, which positively correlat with the cognitive, behavioural and motor deficits of subjects [388]. Studies of treatments designed to lower plasma 5-HT levels were therefore initiated. Early studies with fenfluramine, which is known to reduce brain 5-HT levels after chronic administration [389], reported dramatic effects in three autistic children [390]. However later studies have largely

found no effect of the drug on IQ or maladaptive behaviour and only a slight improvement in apparent developmental age [391]. The non-specific 5-HT antagonist, methysergide [16], was also without significant effect [392]. There is thus little evidence to support a role for 5-HT$_{1C}$ receptor ligands in this disorder at the present time.

Table 6: Affinity of typical and atypical antipsychotic drugs for 5-HT$_{1C}$ and 5-HT$_2$ receptors

Compound	pK$_i$ 5-HT$_{1C}$	pK$_i$ 5-HT$_2$	Selectivity for 5-HT$_2$ over 5-HT$_{1C}$	Class
Loxapine	9.4	8.7	4.7	Typical
Clozapine	8.1	8.3	1.4	Atypical
	8.1[a]	7.6[a]	0.3	
Tiosperone	8.0	10.2	153	Atypical
	7.6[a]	8.5[a]	7.9	
Fluperlapine	7.7	8.1	2.3	Atypical
Rilapine	7.6	9.1	29	Atypical
Chlorpromazine	7.6	8.7	13.5	Typical
	7.9[a]	8.1[a]	1.7	
Risperidone	7.5	9.7	160	Atypical
	7.5[a]	9.2[a]	49	
Setoperone	7.3[b]	8.6[b]	20	Atypical
Spiperone	6.0	9.4	2417	Typical
	6.0[a]	8.8[a]	631	
Amperozide	5.9	7.9	100	Atypical
Melperone	5.9	7.5	42	Atypical

All data from [380] except:
[a] Ref [379]   [b] Ref [16]

Pain

5-HT$_{1C}$ receptors have recently been identified in the spinal cord [393]. Iontophoretic administration of mCPP to dorsal horn nociceptive neurons located within the spinal cord is inhibitory [394]. Systemic administration of mCPP and TFMPP to spinal rats dose-dependently inhibited sensitivity to noxious stimuli which induce the ventroflexion withdrawal reflex [395]. This indicates a spinal or subspinal site of action. The pharmacology of these responses has not been investigated but 5-HT$_{1C}$ receptor medication of antinociception was suggested by McKearney et al. [396]. In this study MK 212, mCPP and TFMPP all increase the shock intensity tolerated by monkeys. This effect was blocked by methysergide a non selective 5-HT$_{1C}$ receptor antagonist (Table 1), but not by the selective 5-HT$_2$ receptor blockers ketanserin or pirenperone. Little human data exists, but, in contrast to the above, ritanserin was reported to increase subjective path thresholds [397]. This effect was modest however and might be related to the migraine prophylactic properties of the drug.

Priapism

MCPP, TFMPP or MK 212 administration causes penile erections in rats. MCPP-induced erections were antagonised by the 5-HT antagonists metergoline, cyproheptadine, mesulergine, mianserin and ritanserin (Table 3, [231]) all of which have high affinity for the $5-HT_{1C}$ site [16]. The 50% inhibitory dose (ID_{50}) values of these drugs were higher than their equivalents against mCPP-induced hypophagia [66] but the rank order of potency was consistent in both paradigms. Ketanserin, the selective $5-HT_2$ antagonist [16], also antagonised mCPP-induced penile erections but only at a relatively high dose [231] consistent with its weak affinity at the $5-HT_{1C}$ site [16] and its rank order of potency against mCPP-induced hypophagia [66]. The more selective $5-HT_2$ receptor antagonist spiperone [16] was inactive [231]. Interestingly, the non-specific $5-HT_2/5-HT_{1C}$ agonist DOI (Table 3) only induced penile erections in the presence of specific $5-HT_2$ receptor antagonists [231] suggesting an interaction between the two sites. MCPP also induced penile erection in rhesus monkeys which was blocked by metergoline [398]. The effect of mCPP may be mediated centrally as penile erections are seen in the rat after intraventricular administration of the 5-HT releasing agent fenfluramine [399], and the 5-HT precursor 5-hydroxytryptophan (5-HTP) is only effective when given with the peripheral decarboxylase inhibitor benserazide (Roche) [400].

In humans, priapism is a major disorder affecting ten million Americans [401]. Penile erection is caused by pooling of blood in the penile blood vessels. In priapism, prolonged stagnation of the pooled blood leads to a fall in oxygen content which increases its viscosity and results in fibrosis and impotence [402]. The condition is therefore considered a urological emergency. 30-50% of cases are drug induced, the most common agents being phenothiazines, butyrophenones, hypnotics (e.g. methaqualone), antihypertensives (eg phenoxybenzamine (SmithKline Beecham), prazosin (Pfizer), hydralazine), anticoagulants (heparin, warfarin) and miscellaneous agents such as ethanol, cannabis, phentolamine (Geigy) and testosterone [402]. Antidepressant therapy is also commonly associated with priapism, most notably with monoamine oxidase inhibitors such as phenelzine and the atypical antidepressant trazodone [402]. Since mCPP is a prominent metabolite of trazodone [56] this may explain its association with priapism, although this has not been reported as a consequence of mCPP administration to man [303]. MAOIs could act in a similar way by potentiating extracellular 5-HT. This may suggest a role for $5-HT_{1C}$ receptor antagonists in the prophylactic or acute treatment of this disorder, at least where caused by antidepressants.
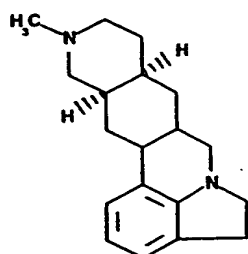
Altered intracranial pressure

The choroid plexus is the major site of formation of cerebral spinal fluid (CSF) in the brain [403,404]. Evidence suggests that 5-HT may control production of CSF, since administration of 5-HT and its precursor 5-HTP [405,406] are inhibitory. 5-HT may reach the choroid plexus from plasma, although concentrations are normally very low [407], or from mast cells found there [408,409]. Evidence also suggests direct serotonergic innervation. Thus moskowitz *et al.* [410] observed the presence of 5-HT that was sensitive to lesions of the raphe nuclei, the site of serotonergic neuronal cell bodies. Using a fluorescence technique that detected indoleamines, Napoleone *et al.* [411] reported that 5-HT neurons were located in the walls of the choroid blood vessels and were also sensitive to raphe cell body lesions. However not all studies have observed 5-HT innervation [412,413]. As has already been described (see above) the choroid plexus contains by far the highest concentration of $5-HT_{1C}$ receptors in any part of the body. It therefore seems likely that they mediate serotonergic control of CSF production as first suggested by Pazos *et al.* [6]. A recent study has shown that SCH 23390 (Schering Plough), a $5-HT_{1C}$ partial agonist [26,414] and dopamine D_1 antagonist [415], markedly
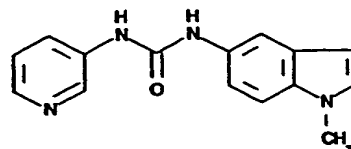
reduces CSF production in rats [416]. Since dopamine D$_1$ sites are not found in the choroid plexus [415] this effect is probably 5-HT$_{1C}$ receptor mediated. These findings therefore suggest that 5-HT$_{1C}$ receptor agonists may be of use in the treatment of patients with increased intracranial pressure such as those with mass lesions, head trauma, acute or hydrocephalus, or pseudotumour cerebri.

Conclusion

5-HT$_{1C}$ receptor antagonists may have therapeutic applications in a number of areas. This possibility rests principally on the reported effects of the putative 5-HT$_{1C}$ receptor agonist mCPP and of the non-specific 5-HT$_2$/5-HT$_{1C}$ receptor antagonists ritanserin and mianserin as opposed to those of the selective 5-HT$_2$ receptor antagonist ketanserin. Unfortunately ketanserin is not entirely selective, possessing significant affinity for α_1 adrenergic receptors [250], a problem also seen with the newer selective 5-HT$_2$ receptor antagonist RP 62203 (Rhone Poulenc) [17]. Spiperone, which has proved of great value in defining 5-HT$_{1C}$ functions *in vitro* due to its one thousand-fold selectivity for the 5-HT$_2$ site, is of little use *in vivo* because of its dopamine D$_2$ receptor antagonist properties. Similarly cisapride (Janssen) has one thousand-fold selectivity for the 5-HT$_2$ site but is also a potent 5-HT$_3$ antagonist and 5-HT$_4$ agonist [417]. Clarification of the therapeutic potential of 5-HT$_{1C}$ receptor modulation should be considerably advanced by the recent development of selective 5-HT$_{1C}$ receptor antagonists by both SmithKline Beecham [500] and Sandoz [501] (Figure 4) and the selective 5-HT$_2$ receptor antagonists RP 62203 [17] and MDL 101151 and its (+) isomer MDL 100907 which both have two hundred- to five hundred-fold selectivity for the 5-HT$_2$ site [418]. However it is also dependent on the pharmacological arguments advanced above, which are principally the result of animal data, being equally valid in humans. This cannot be taken for granted as mesulergine has fifty-fold lower affinity for the human than for the rat 5-HT$_2$ receptor. Thus in humans the drug would have selectivity for the 5-HT$_{1C}$ site [21]. The probability that at least some of the above findings may be attributable to the action of drugs at the rat stomach fundus receptor (see section on receptor distribution), should it be found in human central tissue, cannot be excluded, despite preliminary evidence to the contrary [53,54]. In particular mCPP acts as a weak partial agonist of the rat stomach fundus [48,419] while most 5-HT$_2$/5-HT$_{1C}$ receptor antagonists, but not specific 5-HT$_2$ receptor antagonists, are also antagonists of this site [48]. However current evidence strongly favours a therapeutic role for 5-HT$_{1C}$ receptor ligands in at least some of the indications advanced in this review. Chronic treatment with selective 5-HT reuptake inhibitors is the current therapy of choice in many of these indications (OCD, alcoholism, depression, bulimia) and may become more widely used in others (panic disorder, obesity, migraine). Fluoxetine, the most widely studied drug in this class, is associated with significant side effects (insomnia, nausea, asthenia, tremor and sweating) [79] and may be associated with heightened risk of suicide in depressives [421-423] although these effects have not been reported for other 5-HT reuptake inhibitors. Furthermore, the reuptake inhibitors all require two or more weeks administration for effect. Should down regulation of 5-HT$_{1C}$ receptors be their mode of action, the magnitude of this effect is unlikely to be as pronounced as that caused by an antagonist. Specific 5-HT$_{1C}$ ligands may therefore offer advantages both in the speed of onset of action, efficacy, and side effect profile. Finally, it is conceivable that subtypes of the 5-HT$_{1C}$ receptor may exist, although, with the exception of the rat stomach fundus receptor, there is no evidence of this at present. This might allow differentiation of the anxiogenic and other properties of 5-HT$_{1C}$ receptor agonists facilitating their clinical use.

200646A

Sandoz   SmithKline Beecham

Figure 4: Novel selective 5-HT$_{1C}$ receptor antatagonists

Acknowledgements

References

• = of interest   •• = of considerable interest

1. PEROUTKA SJ, SNYDER SH: **Multiple serotonin receptors: differential binding of [^{3}H]5-hydroxytryptamine, [^{3}H]lysergic acid diethylamide and (^{3}H) spiroperidol.** *Mol. Pharmacol.* (1979) 16:687 -699.

2. PEDIGO NW, YAMAMURA HI, NELSON DL: **Discrimination of multiple [^{3}H] 5-hydroxytryptamine-binding sites by the neuroleptic spiperone in rat brain.** *J. Neurochem.* (1981) 36:220-226.

3. MIDDLEMISS DN, FOZARD RJ: **8-hydroxy-2-(di-n-propylamino)tetralin discriminates between subtypes of the 5-HT$_1$ recognition site.** *Eur. J. Pharmacol.* (1983) 90:151-153.

4. GOZLAN H, EL MESTIKAWAY S, PICHAT L, GLOWINSKI J, HAMON M: **Identification of presynaptic serotonin autoreceptors by a new ligand: [^{3}H]-PAT.** *Nature (London)* (1983) 305:140-142.

5. HOYER D, ENGEL G, KALKMAN HO: **Molecular pharmacology of 5-HT$_1$ and 5-HT$_2$ recognition sites in rat and pig brain membranes: radioligand binding studies with [^{3}H]5-HT, [^{3}H]8-OH-DPAT, (-)[^{125}I]iodocyanopindolol, [^{3}H]mesulergine and [^{3}H]ketanserin.** *Eur. J. Pharmacol.* (1985) 118:13-23.

6. PAZOS A, HOYER D, PALACIOS JM: **The binding of serotonergic ligands to the porcine choroid plexus: characterization of a new type of serotonin recognition site.** *Eur. J. Pharmacol.* (1984) 106:539-546.
•• First identification of the 5-HT$_{1C}$ receptor

7. HEURING RE, PEROUTKA SJ: **Characterization of a novel [^{3}H]5-hydroxytryptamine binding site subtype in bovine brain membranes.** *J. Neurosci.* (1987) 7:894-903.

8. LEONHARDT S, HERRICK-DAVIS K, TITELER M: **Detection of a novel serotonin receptor subtype (5-HT$_{1E}$) in human brain: interaction with a GTP-binding protein.** *J. Neurochem.* (1989) 53:465-471.

9. RICHARDSON BP, ENGEL G, DONATSCH P, STADLER PA: **Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs.** *Nature (London)* (1985) 316:126-131.

10. KILPATRICK GJ, JONES BJ, TYERS MB: **The identification and distribution of 5-HT$_3$ receptors in rat brain using radioligand binding.** *Nature (London)* (1987) 330;746-748.

11. DUMUIS A, BOUHELAL R, SEBBEN M, CORY R, BOCKAERT JA: **A non-classical 5-hydroxytryptamine receptor positively coupled to adenylate cyclase in the central nervous system.** *Mol. Pharmacol.* (1988) 34:880-887.

12. YOUNG WS, KUHAR MJ: **Serotonin receptor localization in rat brain by light microscopic autoradiography.** *Eur. J. Pharmacol.* (1980) 63:237-243.

13. CLOSSE A: **[^{3}H]mesulergine, a selective ligand for serotonin-2 receptors.** *Life Sci.* (1983) 32:2485-2495.

14. LEYSEN JE, NIEMEGEERS CJE, VAN NUETON JM, LADURON PM: **[^{3}H]ketanserin (R41 468), a selective ^{3}H-ligand for serotonin 2 receptor binding sites.** *Mol. Pharmacol.* (1982) 21:301-314.

15. LEYSEN JE, AWOUTERS F, KENNIS L, LADURON PM, VANDENBERK J, JANSSEN PAJ: **Receptor binding profile of R41,468, a novel antagonist of 5-HT$_2$ receptors.** *Life Sci.* (1981) 28:1015-1022.

16. HOYER D: 5-Hydroxytryptamine receptors and
    • effector coupling mechanisms in peripheral
    tissues. In: Fozard J. (ed). Peripheral actions of 5-
    HT. Oxford University Press, Oxford (1989) pp 72-
    99.
    A good review of compound selectivity for 5-HT receptor
    subtypes.

17. DOBLE A, GIRDLESTONE D, PIOT O, ALLAM D,
    BETSCHART J, BOIREAU A, DUPUY A, GUEREMY C,
    MENAGER J, ZUNDEL JL, BLANCHARD JC:
    Pharmacological characterization of RP 62203,
    a novel 5- hydroxytryptamine 5-HT$_2$ receptor
    antagonist. Brit. J. Pharmacol. (1992) 106:7-36.

18. RINALDI-CARMONA M, LONGY C, SANTUCCI J, SIMIAND
    J, GAUTRET B, NELIAT G, LABEEUW B, LE FUR G,
    SOUBRIE P, BRELIERE JC: Biochemical and
    pharmacological properties of SR 46349B, a
    new potent and selective 5-hydroxytryptamine
    receptor antagonist. J. Pharm. Exp. Ther. (1992)
    262:759-768.

19. GLENNON RA, BARTYZEL P, TEITLER M: Binding of
    benz[e]- and benz[g]-fused tryptamine
    derivatives at serotonin receptors: Evidence for
    a region of bulk tolerance. (1992) (in Press).

20. HOYER D, PAZOS A, PROBST A, PALACIOS JM:
    Serotonin receptors in the human brain. II.
    Characterization and autoradiographic
    localization of 5-HT$_{1C}$ and 5-HT$_2$ recognition
    sites. Brain Res. (1986) 376:97-107.

21. KAO H-T, ADHAM N, OLSEN MA, WIEINSHANK RC,
    BRANCHEK TA, HARTIG PR: Site-directed
    mutagenesis of a single residue changes the
    binding properties of the serotonin 5-HT$_2$
    receptor from a human to a rat pharmacology.
    FEBS Lett. (1992) 307:324-328.

22. PALACIOS JM, MARKSTEIN R, PAZOS A: Serotonin-1C
    sites in the choroid plexus are not linked in a
    stimulatory or inhibitory way to adenylate
    cyclase. Brain Res. (1986) 380:151-154.

23. CONN CJ, SANDERS-BUSH E, HOFFMAN BJ, HARTIG PR:
    •• A unique serotonin receptor in choroid plexus
    is linked to phosphatidylinositol turnover.
    Proc. Natl. Acad. Sci. USA (1986) 83:4086-4088.
    First evidence that the 5-HT$_{1C}$ receptor acts through
    phosphatidylinositol hydrolysis.

24. BERRIDGE MJ, IRVINE RF: Inositol triphosphate, a
    novel second messenger in cellular signal
    transduction. Nature (London) (1984) 312:315-
    321.

25. NISHIKUZA Y: The role of protein kinase C in cell
    surface signal transduction and tumour
    promotion. Nature (London) (1984) 308:693-698.

26. HOYER D, WAEBER C, SCHOEFFTER P, PALACIOS JM,
    DRAVID A: 5-HT$_{1C}$ receptor-mediated stimulation
    of inositol phosphate production in pig
    choroid plexus. A pharmacological
    characterization. Naunyn-Schmiedeberg's Arch.
    Pharmacol. (1989) 339:252-258.

27. GUNDERSON CB, MILEDI R, PARKER I: Messenger
    RNA from human brain induces drug- and
    voltage-operated channels in Xenopus oocytes.

    Nature (London) (1984) 308:421-424.

28. LUBBERT H, HOFFMAN BJ, SNUTCH TP, VAN DYKLE T,
    LEVINE AJ, HARTIG PR, LESTER HA, DAVIDSON N:
    cDNA cloning of a serotonin 5-HT$_{1C}$ receptor
    by electrophysiological assays of mRNA-
    injected Xenopus oocytes. Proc. Natl. Acad. Sci.
    USA (1987) 84:4332-4336.

29. LUBBERT H, SNUTCH TP, DASCAL N, LESTER HA,
    •• DAVIDSON N: Rat brain 5-HT$_{1C}$ receptors are
    encoded by a 5-6 kbase mRNA size class and
    are functionally expressed in injected Xenopus
    oocytes. J. Neurosci. (1987) 7:1159-1165.
    Identification of the 5-HT$_{1C}$ receptor mRNA.

30. TAKAHASHI T, NEHER E, SAKMAN B: Rat brain
    serotonin receptors in Xenopus oocytes are
    coupled to endogenous channels. Proc. Natl.
    Acad. Sci. USA (1987) 84:5063-5067.

31. DASCAL N, IFUNE C, HOPKINS R, SNUTCH TP, LUBBERT
    H, DAVIDSON N, SIMON MI, LESTER HA:
    Involvement of a GTP-binding protein in
    mediation of serotonin and acetylcholine
    responses in Xenopus oocytes injected with rat
    brain messenger RNA. Mol. Brain Res. (1986)
    1:201-209.

32. AOSHIMA H, IIO H, ANAN M, KOBAYASHI S:
    Induction of muscarinic acetylcholine,
    serotonin and substance P receptors in
    Xenopus oocytes injected with mRNA prepared
    from the small intestine of rats. Mol. Brain Res.
    (1990) 2:15-27.

33. PANICKER MM, PARKER I, MILEDI R: Receptors of the
    serotonin 1C subtype expressed from cloned
    DNA mediate the closing of K$^+$ membrane
    channels encoded by brain mRNA. Proc. Natl.
    Acad. Sci. USA (1991) 88:2560-2562.

34. GUNDERSON CB, MILEDI R, PARKER I: Serotonin
    receptors expressed by brain mRNA in
    Xenopus oocytes mediate three different ionic
    currents. J. Physiol. (London) (1987) 386:83P.

35. PARKER I, PANICKER MM, MILEDI R: Serotonin
    receptors expressed in Xenopus oocytes by
    mRNA from brain mediate a closing of K$^+$
    membrane channels. Mol. Brain Res. (1990) 7:31-
    38.

36. JULIUS D, MACDERMOTT AB, AXEL R, JESSELL TM:
    •• Molecular characterization of a functional
    cDNA encoding the serotonin 1C receptor.
    Science (1988) 241:558-564.
    Identification of the 5-HT$_{1C}$ receptor cDNA and amino acid
    sequence.

37. SHIH JC, YANG W, CHEN K, GALLAGHER T:
    Molecular biology of serotonin (5-HT)
    receptors. Pharmacol. Biochem. Behav. (1991),
    40:1053-1058.

38. YU L, NGUYEN H, LE H, BLOEM LJ, KOZAK CA,
    HOFFMAN BJ, SNUTCH TP, LESTER HA, DAVIDSON N,
    LUBERT H: The mouse 5-HT$_{1C}$ receptor contains
    eight hydrophobic domains and is X-linked.
    Mol. Brain Res. (1991) 11:143-149.

39. SALTZMAN AG, MORSE B, WHITMAN MM,
    IVANSCHENKO Y, JAYE M, FELDER S: Cloning of the

human serotonin 5-HT$_2$ and 5-HT$_{1C}$ receptor subtypes. *Biochem. Biophys. Res. Commun.* (1991) 181:1469-1478.

40. PRITCHETT DB, BACH AWJ, WOZNY M, TALEB O, DAL TOSO R, SHIH JC, SEEBURG PH: **Structure and functional expression of cloned rat serotonin 5-HT$_2$ receptor.** *EMBO J.* (1988) 7:4135-4140.
 5-HT2 receptor cDNA and amino acid sequence characterized.

41. JARZAB B, DOHLER KD: **Serotonergic influences on sexual differentiation of the rat brain.** *Prog. Brain Res.* (1984) 61:119 -126.

42. PAZOS A, PALACIOS JM: **Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors.** *Brain Res.* (1985) 346:205-230.
 First detailed evidence of the 5-HT$_{1C}$ receptor distribution in central tissue.

43. MENGOD G, NGUYEN H, LE H, WAEBER C, LUBBERT H, PALACIOS JM: **The distribution and cellular localization of the serotonin 1C receptor mRNA in the rodent brain examined by in situ hybridization histochemistry. Comparison with receptor binding distribution.** *Neuroscience* (1990) 35:577-591.

44. PAZOS A, PROBST A, PALACIOS JM: **Serotonin receptors in the human brain-III. Autoradiographic mapping of serotonin-1 receptors.** *Neuroscience* (1987) 21:97-112.

45. HOFFMAN BJ, MEZEY E: **Distribution of serotonin 5-HT$_{1C}$ receptor mRNA in adult rat brain.** *FEBS Lett.* (1989) 247:453-462.
 5-HT$_{1C}$ mRNA distribution in central tissue reported.

46. MOLINEAUX SM, JESSEL TM, AXEL R, JULIUS D: **5-HT$_{1C}$ receptor is a prominent serotonin receptor subtype in the central nervous system.** *Proc. Natl. Acad. Sci. USA* (1989) 86:6793-6797.

47. BUCHEIT KH, ENGEL G, HAGENBACH A, HOYER D, KALKMAN HO, SEILER MP: **The rat isolated stomach fundus strip, a model for 5-HT$_{1C}$ receptors.** *Brit. J. Pharmacol.* (1986) 88:367P.

48. CLINESCHMIDT BV, REISS DR, PETTIBONE DJ, ROBINSON JL: **Characterization of 5-hydroxytryptamine receptors in rat stomach fundus.** *J. Pharmacol. Exper. Ther.* (1985) 235:696-708.

49. COHEN ML, WITTENAUER LA: **Relationship between serotonin and tryptamine receptors in the rat stomach fundus.** *J. Pharmacol. Exp. Ther.* (1985) 233;7579.

50. COHEN ML, WITTENAUER LA: **Serotonin receptor activation of phosphoinositide turnover in uterine, fundal, vascular and tracheal smooth muscle.** *J. Cardiovasc. Res.* (1987) 10:176-181.

51. BAEZ M, YU L, COHEN ML: **Pharmacological and molecular evidence that the contractile response to serotonin in rat stomach fundus is not mediated by activation of the 5-hydroxytryptamine 1C receptor.** *Molec. Pharmacol.* (1990)38:31–37.

52. HARTS J. LIU J, KURSAR JD, BAEZ M, NELSON ML, COHEN ML, YU L: **Serotonin inhibition of cyclic AMP formation in Xenopus oocytes injected with rat stomach fundus RNA.** *Am. Soc. Neurosci. Abstr.* (1991) 17:113.7.

53. FOQUET M, NGUYEN H, LE H, LUBBERT H: **Structure of the mouse 5-HT$_{1C}$, 5-HT$_2$ and stomach fundus serotonin receptor.** *Neuroreport* (1992) 3:345-348.
 Rat stomach fundus (5-HT$_{2B}$) receptor cDNA and amino acid sequence. identified.

54. FOQUET M, HOYER D, PARDO LA, PAREKH A, KLUXEN FW, KALKMAN HO, STUHMER W, LUBBERT H: **Cloning and functional characterization of the rat stomach fundus serotonin receptor.** *EMBO J.* (1992) 11:34381-3487.

55. BERENDSEN HHG, JENCK F, BROEKKAMP CLE: **Involvement of 5-HT$_{1C}$ receptors in drug-induced penile erections in rats.** *Psychopharmacology* (1990) 101:57-61.

56. CACCIA S, BALLABIO M, SAMANIN R, ZANINI MG, GARATTINI S: **mCPP, a central 5-HT agonist, is a metabolite of trazodone.** *J. Pharm. Pharmacol.* (1981) 33:477-478.

57. MARTIN LL, SANDERS-BUSH E: **The serotonin autoreceptor: Antagonism by quipazine.** *Neuropharmacology* (1982) 21:445-450.

58. SILLS MA, WOLFE BB, FRAZER A: **Determination of selective and non-selective compounds for the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes in rat frontal cortex.** *J. Pharmacol. Exp. Therap.* (1984) 231:480-487.

59. KENNETT GA, CURZON G: **Evidence that mCPP may have behavioural effects mediated by 5-HT$_{1C}$ receptors.** *Brit. J. Pharmacol.* (1988) 94:137-147.
 First report of mCPP's 5-HT$_{1C}$ agonist properties in vivo and behavioural consequences.

60. KENNETT GA, CURZON G: **Evidence that hypophagia induced by mCPP and TFMPP requires 5-HT$_{1C}$ and 5-HT$_{1B}$ receptors; hypophagia induced by RU 24969 only requires 5-HT$_{1B}$ receptors.** *Psychopharmacology* (1988) 95:93-100.
 First report that 5-HT$_{1C}$ receptor activation had anorexic effects while blockade was hyperphagic.

61. CONN PJ, SANDERS-BUSH E: **Relative efficacies of piperazines at the phosphoinositide hydrolysis-linked serotonergic (5-HT$_2$ and 5-HT$_{1C}$) receptors.** *J. Pharmacol. Exp. Therap.* (1987) 242:552-557.
 First report of that mCPP was a 5-HT$_{1C}$ receptor agonist in vitro.

62. SCHOEFFTER P, HOYER D: **Interactions of arylpiperazines with 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$ and 5-HT$_{1D}$ receptors: do discriminatory 5HT$_{1B}$ receptor ligand exist?** *Naunyn Schmeidebergs Arch. Pharmacol.* (1989) 339:675-683.

63. BROWN AM, PATCH TL, KAUMANN AJ: **The antimigraine drugs ergotamine and dihydroergotamine are potent 5-HT$_{1C}$ receptor**

agonists in piglet choroid plexus. *Br. J. Pharmacol.* (1991) 104:45-48.

64. SANDERS-BUSH E, BREEDING M: Serotonin 5-HT$_{1C}$ receptor reserve in choroid plexus masks receptor subsensitivity. *J. Pharmacol. Exp. Therap.* (1990) 252:984-988.

65. SIMANSKY KJ, SCHECHTER LE: Dissociation of behavioural properties of 1-arylpiperazines in models for central serotonergic stimulation in rodents. *Fed. Proc.* (1987) 46:966.

66. KENNETT GA, CURZON G: Potencies of antagonists indicate that 5-HT$_{1C}$ receptors mediate 1-2(chlorophenyl)piperazine-induced hypo-phagia. *Brit. J. Pharmacol.* (1991) 103:2016-2020.

67. COHEN ML, FULLER RW: Anatagonism of vascular serotonin receptors by m-chloro-phenylpiperazine and m-trifluorophenyl-piperazine. *Life Sci.* (1983) 32:711-718.

68. ROBERTSON DW, BLOOMQUIST W, WONG DT, COHEN ML: MCPP but not TFMPP is an antagonist at cardiac 5-HT$_3$ receptors. *Life Sci.* (1992) 50:599-605.

69. HARTIG PR, BRANCHEK TA, WEINSHANK RL: A subfamily of 5-HT$_{1D}$ receptor genes. *Trends in Pharmacological Sciences* (1992) 13:152-159.

70. SMITH TM, SUCKOW RF: Trazodone and m-chlorophenylpiperazine. Concentration in the brain and receptor activity in the regions associated with anxiety. *Neuropharmacology* (1985) 24:1067-1071.

71. PETTIBONE DJ, WILLIAMS M: Serotonin-releasing
   • effects of substituted piperazines *in vitro*. *Biochem. Pharmacol.* (1984) 33:1531-1535.
   Evidence of 5-HT releasing properties of mCPP.

72. HAMIK A, PEROUTKA SJ: 1-(m-Chlorophenyl)-piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. *Biol. Psychiat.* (1989) 25:569-575. —

73. MARKS J: The benzodiazepines use, overuse, misuse, abuse. Marks J. (ed). MTP Press Ltd, Lancaster (1985) pp 33-38.

74. SALZMAN L, THALER FH: Obsessive compulsive disorder: a review of the literature. *Am. J. Psychiat* (1981) 138:286-296.

75. ZOHAR J, INSEL TR: Obsessive compulsive disorder: Psychobiological approaches to diagnosis, treatment, and pathophysiology. *Biol. Psychiat* (1987) 22:667-687.

76. EVANS L, KENARDY J, SCHNEIDER P, HOEY H: Effect of a selective serotonin uptake inhibitor in agorophobia with panic attacks. *Acta Psychiat. Scand.* (1986) 73:49-53.

77. GORMAN JM, LIEBOWITZ MR, FYER AJ, GOETZ D, CAMPEAS RB, FYER MA, DAVIEA SO, KLEIN DF: An open trial of fluoxetine in the treatment of panic disorder. *J. Clin. Psychopharmacol.* (1987) 7:329-332.

78. SCHNEIER FR, LIEBOWITZ MR, DAVIES SO, FAIRBANKS J, HOLLANDER E, CAMPEAS R, KLEIN DF: Fluoxetine

in panic disorder. *J. Clin. Psychopharmacol.* (1990) 10:119-121.

79. LEVINE LR, POPE HG, ENAS GG, WILSON MG, BALLENER JC, *et al.*: Fluoxetine in the treatment of Bulimia Nervosa. A multicenter, placebo-controlled, double-blind trial. *Arch. Gen. Psychiat,* (192) 49:139-147.

80. MUELLER EA, MURPHY DL, SUNDERLAND T:
   •• Neuroendocrine effects of m-chlorophenyl-piperazine, a serotonin agonist, in humans. *J. Clin. Endocrinol. Metab.* (1985) 61:1179-1184.
   First report of mCPP's anxiogenic effects in man.

81. CHARNEY DS, WOODS SW, GOODMAN WK, HENINGER
   • GR: Serotonin function in anxiety. II. Effects of the serotonin agonist mCPP in panic disorder patients and healthy subjects. *Psychopharmacology* (1987) 92:14-24.
   MCPP reported to induce panic attacks in panic disorder patients.

82. ZOHAR J, MUELLER EA, INSEL TR, ZOHAR-KADOUCH RC, MURPHY DL: Serotonergic responsivity in obsessive compulsive disorder: comparison of patients and healthy controls. *Arch. Gen. Psychiat.* (1987) 44:946-951.

83. SEIBYL JP, KRYSTAL JH, PRICE LH, WOODS SW,
   •• D'AMICO CD, HENINGER GR, CHARNEY DS: Effects of ritanserin on the behavioural neuroendocrine and cardiovascular responses to meta chlorophenylpiperazine in healthy subjects. *Psychiatry Res.* (1991) 38:227-236.
   Blockade of mCPP-induce anxiety by the non-selective 5-HT$_{1C/2}$ receptor antagonist ritanserin.

84. KAHN RS, WETZLER S, ASNIS GM, KLING MA, SUCKOW
   • RF, VAN PRAAG HM: Effects of m-chlorophenylpiperazine in normal subjects: a dose response study. *Psychopharmacology* (1990) 100:339-344.
   Report of panic attacks in normal volunteers.

85. KALUS O, KAHN RS, WETZLER S, ASNIS GM, VAN PRAAG HM: Behavioural hypersensitivity to m-chlorophenylpiperazine in a subject with subclinical panic attacks. *Biol. Psychiat.* (1990) 28:1053-1057.

86. MURPHY DL, MUELLER EA, HILL JL, TOLLIVER TJ, JACOBSEN FM: Comparative anxiogenic, neuroendocrine and other physiologic effects of m-chlorophenylpiperazine given intravenously or orally to healthy volunteers. *Psychopharmacology* (1989) 98:275-282.

87. MUELLER EA, MURPHY DL, SUNDERLAND T: Further studies of the putative serotonin agonist, m-chlorophenylpiperazine: Evidence for a serotonin receptor mediated mechanism of action in humans. *Psychopharmacology* (1986) 89:388-391.

88. KENNETT GA, WHITTON P, SHAH K, CURZON G:
   •• Anxiogenic-like effects of mCPP and TFMPP in animal models are opposed by 5-HT$_{1C}$ receptor antagonists. *Eur. J. Pharmacol.* (1989) 164:445-454.
   First evidence that 5-HT$_{1C}$ receptors may mediate mCPP-induced anxiogenesis.

89. WHITTON P, CURZON G: Anxiogenic-like effects of infusing 1-(3-chlorophenyl)piperazine (mCPP) into the hippocampus. *Psychopharmacology* (1990) 100:138-140.
Evidence that one site at which mCPP causes anxiety in rats is the hippocampus.

90. GLEESON S, AHLERS ST, MANSBACH RS, ROUST JM, BARRETT JE: Behavioural studies with anxiolytic drugs. IV. Effects on punished responding of drugs interacting with serotonin receptor subtypes. *J. Pharmcol. Exp. Therap.* (1989) 250:809-817.

91. KILTS CD, COMMISSARIS RL, CORDON JJ, RECH RH: Lack of central 5-hydroxytryptamine influence on the anticonflict activity of diazepam. *Psychopharmacology* (1992) 156:375-383.

92. MANSBACH RS, GEYER MA: Blockade of potentiated startle responding in rats by 5-hydroxytryptamine 1A receptor ligands. *Eur. J. Pharmacol.* (1988) 156:373-383.

93. KENNETT GA, BLACKBURN TP: Anxiolytic-like actions of BRL 46470 - a novel 5-HT₃ antagonist. *J. Psychopharmacol.* (1990) 4:4.

94. THOMAS DR, NELSON DR, BLACKBURN TP, WOOD MD: BRL 46470: a novel 5-HT₃ receptor antagonist. *J. Psychopharmacol.* (1990) 4:2.

95. JONES BJ, COSTALL B, DOMENEY AM, KELLY ME, NAYLOR RJ, OAKLEY NR, TYERS MB: The potential anxiolytic activity of GR 38032F, a 5-HT₃-receptor antagonist. *Brit. J. Pharmacol.* (1988) 93:985-993.

96. PIGGOTT TA, ZOHAR J, HILL JL, BERNSTEIN SE, GROVER GN, ZOHAR- KADOUCH RC, MURPHY DL: Metergoline blocks the behavioural and neuroendocrine effects of orally administered m- chlorophenylpiperazine in patients with obsessive-compulsive disorder. *Biol. Psychiat.* (1991), 29:418-426.

97. KAHN RS, KALUS O, WETZLER S, CAHN W, ASNIS GM, VAN PRAAG HM: Effects of serotonin antagonists on m-chlorophenylpiperazine- mediated responses in normal subjects. *Psychiatry Res.* (1990) 33:189-198.

98. KENNETT GA: 5-HT₁C receptor antagonists have anxiolytic-like actions in the rat social interaction model. *Psychopharmacology* (1992) 107:379-384.
Study suggesting that 5-HT₁C receptor antagonists may have anxiolytic properties.

99. KENNETT GA, PITTAWAY K, BLACKBURN TP: Evidence that 5-HT₁C receptor antagonists are anxiolytic in the Geller-Seifter model of anxiety. *Psychopharmacology* (1993) Submitted.

100. HOYER D: Competitive antagonism by recognised 5-HT₂-receptor antagonists at 5-HT₁C receptors. *Naunyn-Schmiedebergs Arch. Pharmacol.* (1990) 341 (suppl):R88.

101. GADIE B, LANE AC, MCCARTHY PS, TULLOCH IF, WALTER DS: 2- Alkyl analogues of RX 781094: a potent selective antagonist at central α₂-

adrenoceptors. *Brit. J. Pharmacol.* (1983) 78:312P.

102. SCHOEFFTER P, HOYER D: 5-Hydroxytryptamine 5-HT₁B and 5-HT₁D receptors mediating inhibition of adenylate cyclase activity. Pharmacological comparison with special reference to the effects of yohimbine, rauwolscine and some β-adrenoceptor antagonists. *Naunyn-Schmiedeberg's Arch. Pharmacol.* (1989) 340:285292.

103. NELSON DR, THOMAS DR: (3-H)-BRL 43694 (Granisetron), a specific ligand for 5-HT₃ binding sites in rat brain cortical membrane. *Biochem. Pharmacol.* (1989) 10:1693-1695.

104. COSTALL B, DOMENEY AM, GERRARD PA, KELLY MA, NAYLOR RJ: Zacopride: Anxiolytic profile in rodent and primate models of anxiety. *J. Pharm. Pharmacol.* (1988)40:302-305.

105. PIPER D, UPTON N, THOMAS DL, NICHOLASS J: The effects of 5-HT₃ receptor antagonists BRL 43694 and GR 38032F in animal models of anxiety. *Brit. J. Pharmacol.* (1988) 94:314P.

106. GARDNER CR: Recent developments in 5-HT-related pharmacology of animal models of anxiety. *Pharmacol. Biochem. Behav.* (1986) 24:1479-1485.

107. COLPAERT FC, MEERT TF, NIEMEGEERS CJE, JANSSEN PAJ: Behavioural and 5-HT antagonist effects of ritanserin: a pure and selective antagonist of LSD discrimination in the rat. *Psychopharmacology* (1985) 86:45-54.

108. DEACON R, GARDNER CF: Benzodiazepine and 5-HT ligands in a rat conflict test. *Brit. J. Pharmacol.* (1986) 88:330P.

109. BROCCO MJ, KOEK W, DEGRYSE A-D, COLPAERT FC: Comparative studies on the anti-punishment effects of chlordiazepoxide, buspirone and ritanserin in the pigeon, Geller-Seifter and Vogel conflict procedures. . *Behav. Pharmacol.* (1990) 1:403-418.

110. NIESINK RJM, VAN REE JM: Antidepressant drugs normalise the increased social behaviour of pairs and male rats induced by short term isolation. *Neuropharmacology* (1982) 21:1343-1348.

111. MASON P, SKINNER J, LUTTINGER D: Two tests in rats for anti- anxiety effect of clinically anxiety attenuating antidepressants. *Psychopharmacology* (1987) 92:30-33.

112. SEPINWALL J, COOK L: Mechanism of action of the benzodiazepines: behavioural aspect. *Fed. Proc.* (1980) 39:3024- 3031.

113. BECKER HC: Comparison of the effects of the benzodiazepine midazolam and three serotonin antagonists on a consumatry conflict paradigm. *Pharmacol. Biochem. Behav.* (1986) 24:1057- 1064.

114. KOEK W, JACKSON A, COLPAERT FC: Behavioural pharmacology of antagonists at 5-HT₂/5-HT₁C receptors. *Neurosci. Biobehav. Rev.* (1993) 16:95-

105.

115. FILE SE: Metabolism disorders of the central nervous system. Clifford Rose, (ed). Pitmans, London, pp 420-445.

116. WINTER JD: Comparison of chlordiazepoxide, methysergide and cinanserin as modifiers of punished behaviour and as antagonists of N,N-dimethyltryptamine. Arcb. Int. Pharmacodyn. Ther. (1972) 197:147-159.

117. GRAEFF FG: Tryptamine antagonists and punished behaviour. J. Pharmacol. Exp. Therap. (1974) 189:344-350.

118. COOK K, SEPINWALL J: Mechanisms of action of benzodiazepines. (1975). Costa E, Greengard P, (Eds). Raven Press, New York, pp 1-28.

119. STEIN L, WISE CD, BELLUZZI JD: Mechanisms of action of the benzodiazepines. (1975) Costs E, Greengard P, (Eds), Raven Press, New York, pp 29-44.

120. LEONE CML, DE AGUIR JC, GRAEFF FG: Role of 5-hydroxytryptamine in amphetamine effects on punished and unpunished behaviour. Psychopharmacology (1983) 80:78-82.

121. NASHOLD BS, WILSON WP, SLAUGHTER DG: Sensations evoked by stimulation of the midbrain of man. J. Neurosurg. (1969) 30:14-24.

122. OLDS ME, OLDS J: Approach-avoidance analysis of rat diencephalon. J. Comp. Neurol. (1963) 120:359-295.

123. JENCK F, BROEKKAMP CLE, VAN DELFT ML: 5-HT$_{1C}$ receptors in the serotonergic control of periaqueductal gray induced aversion in rats. Psychopharmacology (1990) 100;372-376.

124. BECKETT SRG, MARSHALL PW, MARSDEN CA: Intra -
• Periaqueductal Grey administration of mCPP potentiates a chemically-induced defence response. Brit. J. Pharmacol. (1992) 107 (suppl 1):8P.
Identification of the periaqueductal grey as a second site which may mediate mCPP-induced anxiety.

125. MURPHY JE: Mianserin in the treatment of depressive illness and anxiety states in general practice. Brit. J. Pharmacol. (1978) 5:81S-85S.

126. RUSSEL GFM, NIAZ U, WAKELING A, SLADE PD: Comparative double-blind trial of mianserin hydrochloride (Organon GB94) and diazepam in patients with depressive illness. Brit. J. Clin. Pharmacol. (1978) 5:57S-65S.

127. CONTI L, PINDER RM: A controlled comparative trial of mianserin and diazepam in the treatment of anxiety states in psychiatric outpatients. Int. J. Med. Res. (1979) 7:285-289.

128. KHAN MC, BENNIE EH, STULEMEIJER SM, RAVENS MA: Mianserin and dioxepin in the treatment of outpatient depression with anxiety. Brit. J. Clin. Pharmacol. (1983) 15:213S-218S.

129. CEULEMANS DLS, HOPENBROUWERS MLJA, GELDERS
•• YG, REYNTJENS AJM: The influence of ritanserin, a serotonergic antagonist, in anxiety disorders: a double-blind placebo-controlled study versus lorazepam. Pharmacopsychiatry (1985) 18:303-305.
Clinical evidence of the antianxiety properties of a 5-HT$_{1C/2}$ receptor antagonist.

130. BRESSA GM, MARINI S, GREGORI S: Serotonin S2 receptor blockade and generalised anxiety disorder. A double blind study on ritanserin and lorazepam. In. J. Clin. Pharm. Res. (1987) VII:111-119.

131. PANGALILA-RATU LANGI EA, JANSSEN AI: Ritanserin the treatment of generalised anxiety disorders: a placebo-controlled trial. Human Psychopharmacology (1988) 3:207-212.

132. GRAEFF FG, ZUARDE AW, GIGLIO JS, LIMA FILHO EC, KARNIOL IG: Effect of metergoline on human anxiety. Psychopharmacology (1985) 86:334-338.

133. KAHN RS, ASNIS GM, WETZLER S, VAN PRAAG HM: Neuroendocrine evidence for serotonin receptor supersensitivity in patients with panic disorder. Psychopharmacology (1988) 96:360-364.

134. KAHN RS, WETZLER S, VAN PRAAG HM, ASNIS GM: Behavioural indications of serotonin receptor hypersensitivity in patients with panic disorder. Psychiatr. Res. (1988) 25:101-104.

135. KLEIN E, ZOHAR J, GERACI MF, MURPHY DL, UHDE TW: Anxiogenic effects of mCPP in patients with panic disorder: comparison to caffeine's anxiogenic effects. Biol. Psychiat. (1991) 30:973-984.

136. KAHN RS, WETZLER S, ASNIS GM, KLING MA, SUCKOW RF, VAN PRAAG HM: Pituitary hormone responses to m-chlorophenylpiperazine in patients with panic disorder and healthy subjects. Psychiat. Res. (1991) 37:25-34.

137. CHARNEY DS, HENINGER GR, JATLOW PI: Increased anxiogenic effects of caffeine in panic disorders. Arcb. Gen. Psychiat. (1985) 42:233-243.

138. UHDE TW: Neurobiological aspects of panic disorder. Ballenger JC (Ed). Alan Liss, New York, pp 219-242.

139. CHARNEY DS, HENINGER GR, BREIER A: Noradrenergic function in panic disorder: Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. Arcb. Gen. Psychiat. (1984) 41:751-763.

140. LIEBOWITZ MR, FYER AG, GORMAN JM: Lactate provocation of panic attacks. L Clinical and behavioural findings. Arcb. Gen. Psychiat. (1984) 41:764-770.

141. WESTENBERG HGM, DEN BOER JA: Serotonin-
•• influencing drugs in the treatment of panic disorder. Psychopathology (1989) 22 (suppl):68-77.
Failure of a 5-HT$_{1C/2}$ receptor antagonist to ameliorate panic disorder.

142. GRIEZ E, POLS H, LOUSBERG H: Serotonin antagonism in panic disorder: an open trial with ritanserin. *Acta. Psychiat. Belg.* (1988) 88:372-377.

143. INSEL TR, MURPHY DL, COHEN RM, ALTERMAN I, KILTS C, LINNOILA M: Obsessive-compulsive disorder: a double-blind trial of clomipramine and clorgyline. *Arch. Gen. Psychiat.* (1983) 40:605-612.

144. THOREN P, ASBERG M, CRONHOLM B, JORNSTEDT L, TRASKMAN L: Clomipramine treatment of obsessive compulsive disorder. I. A controlled clinical trial. *Arc. Gen. Psychiat.* (1980) 37:1281-1285.
Identification of the clinical efficacy of 5-HT reuptake inhibitors in OCD.

145. MURPHY DL, PIGGOTT TA: A competitive examination of a role for serotonin in obsessive compulsive disorder, panic disorder and anxiety. *J. Clin. Psychiat.* (199) 5 (5, suppl):53-58.

146. ZAK JP, MILLER JA, SHEEHAN DV, BALSAM SLF: The potential role of serotonin uptake inhibitors in the treatment of obsessive compulsive disorder. *J. Clin. Psychiat.* (1988) 49 (8, suppl):23-29.

147. YARYURA-TOBIAS JS, BHAGAVAN HN: L-tryptophan in obsessive- compulsive disorders. *Am. J. Psychiat.* (1977) 234:1298-1299.

148. THOREN P, ASBERG M, BERTILSSON L, MELLSTROM B, SJOQVIST F, TRASKMAN L: Clomipramine treatment of obsessive compulsive disorder. II. Biochemical aspects. *Arch. Gen. Psychiat.* (1980) 37:1289-1294.

149. INSEL TR: New pharmacological approaches to obsessive compulsive disorder. *J. Clin. Psychiat.* 51 (10, suppl) (1990):47- 51.

150. CHOUINARD G, GOODMAN W, GREIST J, JENIKE M, RASMUSSEN S, WHITE K, HACKETT E, GAFFNEY M, BICK PA: Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive-disorder. *Psychopharmacology Bull.* (1990) 26:279-284.

151. HOLLANDER E, DeCARIA CM, SCHNEIER FR, SCHNEIER HA, LIEBOWITZ MR, KLEIN DF: Fenfluramine augmentation of serotonin reuptake blockade antiobsessional treatment. *J. Clin. Psychiat.* (1990) 51:119-123.

152. ZOHAR J, MUELLER EA, INSEL TR, ZOHAR-KADOUCH RC, MURPHY DL: Serotonergic responsivity in obsessive compulsive disorder: Comparison of patients and healthy controls. *Arch. Gen. Psychiat.* (1987) 44:946-951.
MCPP causes OCD symptoms in OCD patients.

153. HOLLANDER E, FAY M, COHEN B, CAMPEAS R, GORMAN JM, LIEBOWITZ MR: Serotonergic and noradrenergic sensitivity in obsessive-compulsive disorder: Behavioural findings. *Am. J. Psychiat.* (1988) 145:1015-1018.

154. HOLLANDER E, DeCARIA CM, NITESCU A, GULLY R, SUCKOW RF, COOPER TB, GORMAN JM, KLEIN DF, LIEBOWITZ MR: Serotonin function in obsessive-compulsive disorder. Behavioural and neuroendocrine responses to oral m-chlorophenylpiperazine and fenfluramine in patients and healthy volunteers. *Arch. Gen. Psychiat.* (1992) 49:2128.

155. CHARNEY DS, GOODMAN WK, PRICE LH, WOODS SW, RASMUSSEN SA, HENINGER GR: Serotonin function in obsessive-compulsive disorder: A comparison of the effects of tryptophan and m-chlorophenylpiperazine in patients and healthy subjects. *Arch. Gen. Psychiat.* (1988) 45:177-185.

156. BASTANI B, NASH JF, METZER HY: Prolactin and cortisol responses to MK-212, a serotonin agonist, in obsessive-compulsive disorder. *Arch. Gen. Psychiat.* (1990) 47:833-839.
Failure of MK-212, a 5-HT$_{1C}$ receptor agonist, to elicit OCD symptoms in OCD patients.

157. HOLLANDER E, DeCARIA C, GULLY R, NITESCU A, SUCKOW RF, GORMAN JM, KLEIN DF, LIEBOWITZ MR: Effects of chronic fluoxetine treatment on behaviour and neuroendocrine responses to meta- chlorophenylpiperazine in obsessive-compulsive disorder. *Psychiat. Res.* (1990) 36:1-17.

158. ZOHAR J, INSEL TR, ZOHAR-KADOUCH RC, HILL JL, MURPHY DLL: Serotonergic responsivity in obsessive-compulsive disorder: Effects of chronic clomipramine treatment. *Arch. Gen. Psychiat.* (1988) 45:167-172.
Desensitiztion of responses to the 5-HT$_{1C}$ receptor agonist mCPP in OCD patients after chronic treatment with the clinically efficious 5-HT reuptake inhibitor, chlorimipramine.

159. GLENNON RA, ISMAIEL AE-KM, McCARTHY BG, PEROUTKA SJ: binding of arylpiperazines to 5-HT$_3$ serotonin receptors: results of a structure affinity study. *Eur. J. Pharmacol.* (1989) 168:387-392.

160. CUNNINGHAM KA, CALLAHAN PM, APPEL JB: Discriminative stimulus properties of the serotonin agonist MK 212. *Psychopharmacology* (1986) 90:193-197.

161. McBRIDE PA, DeMEO MD, SWEENEY JA, HALPER J, MANN JJ, SHEAR MK: Neuroendocrine and behavioural responses to challenge with the indirect serotonin agonist dl-fenfluramine in adults with obsessive-compulsive disorder. *Biol. Psychiat.* (1992) 31:19-34.

162. CRONIN SM, BILL DJ, FLETCHER A: Evidence for the involvement of 5-HT$_{1C}$ receptors in the anxiogenic-like effects of fenfluramine in a modified Vogel conflict test. *Brit. J. Pharmacol.* (1992) (in press).
Further evidence of the anxiogenic effects of 5-HT$_{1C}$ receptor activation.

163. MENINI T, BIZZI A, CACCIA S, CODEGONI A, FRACASSO C, RITTOLI E, GUISO G, PADURA IM, TADDEI C, USLENGHI A, GARATTII S: Comparative studies on

the anorectic activity of d-fenfluramine in mice, rats, and guinea pigs. *Naunyn Schmiedebergs Arch. Pharmacol.* (1991) 343:483-490.

164. RASMUSSEN SA, GOODMAN WK, WOODS SW, HENINGER GK, CHARNEY DS: **Effects of yohimbine in obsessive-compulsive disorder.** *Psychopharmacology* (1987) 93:308-313.

165. GORMAN JM, LIEBOWITZ MR, FYER AJ, DILLON D, DAVIES SO, STEIN J, KLEIN DF: **Lactate infusions in obsessive-compulsive disorder.** *Am. J. Psychiat.* (1985) 142:864-866.

166. ZOHAR J, KLEIN EM, MUELLER EA, INSEL TR, UHDE TW, MURPHY DL: **5HT, obsessive-compulsive disorders and anxiety.** *Am. Psychiat. Assoc.* Chicago (1987)111.

167. BENKELFAT C, MURPHY DL, ZOHAR J, HILL JL, GROVER G, INSEL TR: **Clomipramine in obsessive-compulsive disorder. Further evidence for a serotonergic mechanism of action.** *Arch. Gen. Psychiat.* (1989) 46:23-26.

168. SCHOEFFTER I, WAEBER C, PALACIOS JM, HOYER D: **The 5- hydroxytryptamine 5-HT$_{1D}$ receptor subtype is negatively coupled to adenylate cyclase in calf substantia nigra.** *Naunyn Schmiedebergs Arch. Pharmacol.* (1988) 337:602-608.

169. ZOHAR J, KINDLER S: **Serotonergic probes in obsessive compulsive disorder.** *Int. Clin. Psychopharmacol.* (1992) Suppl. 1:39-40.

170. ROBINS LN, HELZER JE, WEISSMAN MM, ORVASCHEL H, GRUENBERG E, BURKE JD, REGIER DA: **Lifetime prevalence of specific psychiatric disorders in three sites.** *Arch. Gen. Psychiat.* (1984) 41:949-958.

171. BALLENGER JC, GOODWIN FK, MAJOR LF, BROWN GL: **Alcohol and central serotonin metabolism in man.** *Arch. Gen. Psychiat.* (1979) 36:224-227.

172. ROY A, VIRKUNNEN M, LINNOILA M: **Reduced central serotonin turnover in a subgroup of alcoholics.** *Prog. Neuropsychopharmacol. Biol. Psychiat.* (1987) 11:173-177.

173. TAKAHASHI S, YAMANE H, KONDO H, TANI N, KATO N: **CSF monoamine metabolites in alcoholism, a comparative study with depression.** *Folia Psychiatrica et Neurologia Japanica* (1974) 28:237-354.

174. BANKI CM: **5-Hydroxytryptamine content of the whole blood in psychiatric illness and alcoholism.** *Acta. Psychiat. Scand.* (1978) 57:232.

175. BANKI CM: **Factors influencing monoamine metabolites and tryptophan in patients with alcohol dependence.** *J. Neural Transm.* (1981) 50:98-101.

176. MCBRIDE WJ, MURPHY JM, LUMENG L, LI TK: **Serotonin, dopamine and GABA involvement in alcohol drinking of selectively bred rats.** *Alcohol* (1990) 7:199-205.

177. HOLMAN RB, SNAPE BM: **Effects of ethanol on 5-hydroxytryptamine release from corpus**

striatum in vivo. *Alcohol* (1985) 2:249-253.

178. TYTELL M, MYERS RD: **Metabolism of [^{14}C]-serotonin in the caudate nucleus, hypothalamus and reticular formation of the rat after ethanol administration.** *Biochem. Pharmacol.* (1973) 2:361-372.

179. MURPHY JM, MCBRIDE WJ, GATTO GJ, LUMENG L, LI TK: **Effects of acute ethanol administration of monoamine and metabolite content in forebrain regions of ethanol-tolerant and nontolerant alcohol preferring (P) rats.** *Pharmacol. Biochem. Behav.* (1988) 29:169-174.

180. MORINAN A: **Reduction in striatal 5-hydroxytryptamine turnover following chronic administration of ethanol to rats.** *Alcohol* (1987) 22:53-60.

181. ZABIK JK, BINKENDO K, ROACHE JD: **Research advances in new psychopharmacologic treatment for alcoholism.** Naranjo CA, Sellers EM, (Eds). Elsevier, Amsterdam, (1985), pp 75-93.

182. GORELICK DA: **Effects of fluoxetine on alcohol consumption.** *Alcohol* (1986) 10:113.

183. MURPHY JM, MCBRIDE WJ, LUMENG L, LI TK: **Effects of serotonergic agents on ethanol intake of the high alcohol drinking (HAD) line of rats.** *Pharmacol. Biochem. Behav.* (1987) 26:389-392.

184. MURPHY JM, WALLER MB, GATTO GJ, MCBRIDE WJ, LUMENG L, LI TOK: **Effects of fluoxetine on the intragastric self- administration of EtOH in the alcohol preferring P line of rats.** *Alcohol* (1988) 5:283-286.

185. GILL K, FILION Y, AMIT Z: **A further examination of the effects of sertraline on voluntary ethanol consumption.** *Alcohol* (1988) 5:355-358.

186. LEVY A, MCBRIDE WJ, MURPHY JM: **Effects of intra-accumbens infusions of DA and 5-HT on ethanol intake of alcohol-preferring (P) rats (abstract).** *Alcoholism* (1989) 13:305.

187. SVENSSON L, ENGEL J, HARD E: **Effects in the 5-HT receptor agonist 8-OH-DPAT on EtOH preference in the rat.** *Alcohol* (1989) 6:17-21.

188. PRIVETTE TH, HORNSBY RL, MYERS RD: **Buspirone alters alcohol drinking induced in rats by tetrahydropapaveroline injected into brain monoaminergic pathways.** *Alcohol* (1987) 5:147-152.

189. WALTERS JK: **Effects of PCPA on the consumption of alcohol, water and other solutions.** *Pharmacol. Biochem. Behav.* (1977) 6:377383.

190. PARKER LF, RADOW BL: **Effects of parachlorophenylalanine on ethanol self-selection in the rat.** *Pharmacol. Biochem. Behav.* (1976) 4:535-540.

191. ROCKMAN GE, BROWN ZW, BOURQUE C, OGREN S-O: **An investigation of the mechanism of action of 5-hydroxytryptamine in the suppression of ethanol intake.** *Neuropharmacology* (1982) 21:341-347.

192. WEISS F, MITCHENER M, BLOOM FE, KOOB GF: Free-choice responding for ethanol versus water in alcohol preferring (P) and unselected Wistar rats is differentially modified by naloxone, bromocriptine and methysergide. *Psychopharmacology* (1990) 101:178-186.

193. HO AKS: Experimental studies on alcoholism I. Increase in alcohol preference by 5,6,dihydroxytryptamine and brain acetyl-choline. *Psychopharmacology* (1974) 40:101-107.

194. KIIANMAA K: Alcohol intake in the rat after lowering brain 5-hydroxytryptamine content by electrolytic midbrain raphe lesions, 5,6-dihydroxytryptamine or p-chlorophenyl-alanine. *Med. Biol.* (1976) 54:203-209.

195. NARANJO CA, SELLERS EM: Recent developments in alcoholism. (Vol &). Galanter M (Ed), Plenum, (1989) pp 255-266.

196. NARANJO CA, POULOS CX, BREMNER KE, LANETOT KL: Citalopram decreases desireability, liking, and consumption of alcohol in alcohol-dependent drinkers. *Clin. Pharmacol. Ther.* (1992) 51:729-939.

197. GERRA G, CACCAVARI R, DELSIGNORE R, BOCCHI R, FERTONANI G, PASSERI M: Effects of fluoxetine and CA-acetyl homotaurinate on alcohol intake in familial and non-familial alcoholic patients. *Curr. Therap. Res.* (1992) 52:291-295.

198. BRUNO F: Buspirone in the treatment of alcoholic patients. *Psychopharmacology* (1989) 22 (suppl):49-59.

199. OLIVERA AA, SARVIS S, HEARD C: Anxiety disorders coexisting with substance dependence: treatment with buspirone. *Curr. Therap. Res.* (1990) 47:52-60.

200. TOLLEFSON GD, MONTAGUE-CLOUSE J, LANCASTER SP: Buspirone in comorbid alcohol dependency and generalized anxiety disorders. *Drug Therapy* (1990) 20 (Suppl):35-50.

201. DEMONTIGNY C, BLIER P, CHAPUT Y: Electrophysiologically identified serotonin receptors in the cat CNS-effect of antidepressant treatment. *Neuropharmacology* (1984) 23:1511-1519.

202. BENKELFAT C, MURPHY DL, HILL JL, GEORGE DT,
•• NUTT D, LINNOILA M: Ethanol like properties of the serotonergic partial agonist m-chlorophenylpiperazine in chronic alcoholic patients. *Arch. Gen. Psychiat.* (1991) 48:383.
MCPP reported to induce craving in withdrawn alcoholics.

203. SELLERS EM, HIGGINS GA, SOBELL MB: 5-HT and
• alcohol abuse. *Trends in Pharmacol. Sci* (1992) 13:69-75.
Review of the role of 5-HT in the effects of alcohol.

204. SIGNS SA, SCHECHTER MD: The role of dopamine and serotonin receptors in the mediation of the ethanol interoceptive cue. *Pharmacol. Biochem. Behav.* (1988) 30:55-64.

205. KENNETT GA, DOURISH CT, CURZON G: 5-HT$_{1B}$ agonists induce anorexia at a postsynaptic site.

Eur. J. Pharmacol. (1987) 141:429-435.

206. MODELL JG, MOUNTZ JM, BEESFORD TP: Basal ganglia/limbic striatal and thalamocortical involvement in craving and loss of control in alcoholism. *J. Neuropsychiat. Clin. Neurosci.* (1990) 2:123-144.

207. KUSHNER MG, SHER KJ, BEITMAN BD: The relation between alcohol problems and the anxiety disorders. *Am. J. Psychiat.* (1990) 147:685-695.

208. GOLDBERG HL, FINNERTY RJ: The comparative efficacy of buspirone and diazepam in the treatment of anxiety. *Am. J. Psychiat.* (1979) 136:1184-1187.

209. MEERT TF, JANSSEN PAJ: Ritanserin, a new
•• therapeutic approach for drug abuse. Part 1: Effects on alcohol. *Drug Development Res.* (1991) 24:235-249.
Evidence that a 5-HT$_{1C/2}$ receptor antagonist may reduce alcohol preference in rats.

210. KENNETT GA, D'ARCY S, BLACKBURN TP: Effect of 5-HT receptor antagonists on rat ethanol preference. *J. Psychopharmacol.* (1992) Abstr. BAP/EPBS meeting. A76.

211. MONTI JM, ALTERWAIN P: Ritanserin decreases
•• alcohol intake in chronic alcoholics. *Lancet* (1991) 337:60.
A 5-HT$_{1C/2}$ receptor antagonist was reported to reduce alcohol intake in alcoholics.

212. SCHECHTER LE, SIMANSKY KT: 1-(2,5-Dimethoxy-4-iodophenyl)-2- aminopropane (DOI) exerts an anorexic action that is blocked by 5-HT$_2$ antagonists in rats. *Psychopharmacol.* (1988) 94:342-346.

213. LUCKI I, FRAZER A: Behavioural effects of indole and piperazine type serotonin receptor antagonists. *Am. Soc. Neurosci.* (1982) 8 (Abstr):101.

214. SADZOT B, BARABAN JM, GLENNON RA, LYON RA, LEONHEART S, JAN CR, TITELER M: Hallucinogenic drug interactions at human brain 5- HT$_2$ receptors: implications for treating LSD-induced hallucinogenesis. *Psychopharmacology* (1989) 98:495-499.

215. MEERT TF, AWOUTERS F, NIEMEGEERS CJE, SCHELLEKENS KHL, JANSSEN PAJ: Ritanserin reduces abuse of alcohol, cocaine, and fentanyl in rats. *Pharmacopsychiat.* (1991) 24:159-163.

216. MEERT TF, JANSSEN PAJ: Ritanserin, a new
• therapeutic approach for drug abuse. Part 2: Effects on cocaine. *Drug Development Res.* (1991) 25:39-53.
This data suggests that the effects of a 5-HT$_{1C}$ receptor antagonist on alcohol may also apply to cocaine preference in rats. This type of drug may therefore inhibit addiction to other drugs of abuse.

217. MEERT TF, JANSSEN PAJ: Ritanserin, a new therapeutic approach for drug abuse. Part 3: Effects on fentanyl and sucrose. *Drug Development Res.* (1991) 25:55-66.

218. IMPERATO A, DI CHIARA G: **Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol.** *J. Pharmacol. Exp. Therap.* (1986) 239:219-228.

219. VAN PRAAG HM, KAHN RS, ASNIS GM, WETZLER S, BROWN SL, BLEICH A, KORN ML: **New concepts in depression.** Pierre Fabre monograph series 2. Macmillan (1988), pp 96-119.

220. CAMARA EG: **Open study on the use of cyproheptadine in hypercortisolaemic, unipolar, depressed patients.** *Biol. Psychiat.* (1991) 29:201A.

221. REYNTJENS A, GELDERS YG, HOPPENBROUWERS M-LJA,
• BUSSCHE GV: **Thymosthenic effects of ritanserin (R 55667), a centrally acting serotin-S2 receptor blocker.** *Drug Dev. Res.* (1986) 8:205-211.
A 5-HT$_{1C/2}$ receptor antagonist reported to have antidepressant-like properties.

222. KLIESER E, STRAUSS WH: **Study to establish the indication for the selective S2-antagonist ritanserin.** *Pharmacopsychiat.* (1988) 21:391-393.

223. NAPPI G, SANDRINI G, GRANELLA F, RUIZ L, CERUTTI
• G, FRACCHINETTI F, BLANDINI F, MANZONI GC: **A new 5-HT$_2$ antagonist (Ritanserin) in the treatment of chronic headache with depression. A double-blind study vs amitryptyline.** *Headache* (1990) 30:439-444.
Reported efficacy of a 5-HT$_{1C/2}$ receptor antagonist in migraine.

224. LAWLOR BA, SUNDERLAND T, MELLOW AM, HILL JL, NEWHOUSE PA, MURPHY DL: **A preliminary study of the effects of intravenous m-chlorophenyl-piperazine, a serotonin agonist, in elderly subjects.** *Biol. Psychiat.* (1989) 25:679-686.

225. LAWLOR BA, SUNDERLAND T, MELLOW AM, HILL JL, MOLCHAN SE, MURPHY DL: **Hyperresponsivity to the serotonin agonist, m-chlorophenyl-piperazine in Alzheimer's disease.** *Arch. Gen. Psychiat.* (1989) 46:542-549.

226. KAHN RS, WTZLER S, ASNIS GM, PAPOLOS D, VAN PRAAG HM: **Serotonin receptor sensitivity in major depression.** *Biol. Psychiat.* (1990) 28:358-362.

227. MELLOW AM, LAWLOR BA, SUNDERLAND T, MUELLER
• EA, MOLCHAN SE, MURPHY DL: **Effects of daily oral m-chlorophenylpiperazine in elderly depressed patients. Initial experience with a serotonin agonist.** *Bio. Psychiat.* (1990) 28:588-594.
Interesting antidepressant response to subchronic mCPP.

228. ANDERSON JL: **Serotonin receptor changes after chronic antidepressant treatments: ligand binding, electrophysiological and behavioral studies.** *Life Sci.* (1983) 32:1791-1801.

229. LUCKI I, WARD HA, FRAZER A: **Effect of 1-(m-chlorophenyl)piperazine and 1-(m-trifl-uoromethylphenyl)piperazine on locomotor activity.** *J. Pharmacol. Exp. Therap.* (1989) 249:155- 164.

230. BERENDSEN HHG, BROEKAMP CLE: **Attenuation of 5-**

HT$_{1A}$ and 5-HT$_2$ but not 5-HT$_{1C}$ receptor mediated behaviour in rats following chronic treatment with 5-HT receptor agonists, antagonists or antidepressants. *Psychopharmacology* (1991) 105:219-224.

231. BERENDSEN HHG, JENCK F, BROEKAMP CLE:
• **Involvement of 5-HT$_{1C}$ receptors in drug-induced penile erections in rats.** *Psychopharmacology* (1990) 101:57-61.
5-HT$_{1C}$ receptor activation reported to mediate penile erection in rats.

232. COHEN RM, AULAKH CS, MURPHY DL: **Long term**
• **clorgyline treatment antagonizes the eating and motor function responses to m-chlorophenylpiperazine.** *Eur. J. Pharmacol* (1983) 94:175-179.
First data suggesting that antidepressants may desensitize 5-HT$_{1C}$ receptors.

233. WOZNIAK KM, AULAKH CS, HILL JL, MURPHY DL:
• **Hyperthermia induced by m-CPP in the rat and its modification by antidepressant treatments.** *Psychopharmacology* (1989) 97:269-274.
Evidence that mCPP-induced hyperthermia in rats may be 5-HT$_{1C}$ receptor mediated.

234. MAJ J, MORYL E: **Effects of sertraline and citalopram given repeatedly on the responsiveness of 5-HT receptor populations.** *J. Neural. Transm.* (1992) 88:143-156.

235. AULAKH CS, COHEN RM, HILL JL, MURPHY DL, ZOHAR J: **Long-term imipramine treatment enhances the locomotor and food intake suppressant effects of m-CPP in rats.** *Brit. J. Pharmacol.* (1987) 91:747-752.

236. AULAKH CS, HAASS M, ZOHAR J, WOZNIAK KM, HILL JM, MURPHY DL: **Long term imipramine treatment potentiates m- chlorophenyl-piperazine-induced changes in prolactin but not corticosterone or growth hormone levels in rats.** *Pharmacol. Biochem. Behav.* (1989) 32:37-42.

237. SILLS MA, LUCKI I, FRAZER A: **Development of selective serotonin behavioural syndrome and suppression of either 5-MEODMT or mCPP.** *Life Sci.* (1985) 36:2463-2469.

238. FREO U, HOLLOWAY HW, GRIEG NH, SONCRANT TT: **Chronic treatment with meta-chlorophenylpiperazine (m-CPP) alters behavioral and cerebral metabolic responses to the serotonin agonists mCPP and quipazine but not 8-hydroxy-2(di-N-propylamino)tetralin.** *Psychopharmacology* (1992) 107:30-38.

239. ULRICHSEN J, PARTILLA JS, DAX EM: **Long term administration of m-chlorophenylpiperazine (mCPP) to rats induces changes in serotonin receptor binding, dopamine levels and locomotor activity without altering prolactin and corticosterone secretion.** *Psychopharmacology* (1992) 107:229-235.

240. WONG DT, THRELKELD PG, ROBERTSON DW: **Affinities of fluoxetine, its enantiomers and other inhibitors of serotonin uptake for subtypes of serotonin receptors.**

Neuropsychopharmacology (1991) 5:43–47.

241. BREWERTON TD, MURPHY DL, MUELLER EA, JIMERSON DC: Induction of migraine-like headaches by the serotonin agonist m-chlorophenyl-piperazine. *Clin. Pharmacol. Ther.* (1988) 43:605-609.
MCPP reported to induce migraine-like headaches particularly in migraineurs.

242. GORDON ML, LIPTON RB, BROWN SL: A neuroendocrine challenge study with mCPP in migraine subjects and normal controls. *Cephalalgia* (1992) (in press).

243. FOZARD JR, GRAY JA: 5-HT$_{1C}$ receptor activation: a key step in the initiation of migraine? *Trends in Pharmacol. Sci.* (1989) 10:307-309.
Hypothesis of 5-HT$_{1C}$ receptor activation causing and preventing migraine proposed

244. WINTHER K: Ketanserin, a selective serotonin antagonist, in relation to platelet aggregation and migraine attack rate. *Cephalalgia* (1985) 5 (suppl 3):402-403.

245. BOWMAN WC, RAND MJ: Textbook of pharmacology. Blackwell Scientific Publications, Oxford (1980).

246. DOENICKE A, BRAND J, PERRIN V: Possible benefit of GR 43175, a novel 5-HT$_1$-like receptor agonist, for the acute treatment of severe migraine. *Lancet* (1988) 1:1309-1311.

247. HUMPHREY PPA: 5-Hydroxytryptamine and the pathophysiology of migraine. *J. Neurol.* (1991) 238:S38-S44.

248. FOZARD JR: 5-HT in migraine. In Sandler M, Collins GM (eds). Migraine: a spectrum of ideas. Oxford University Press, Oxford (1990) pp 128-146.

249. DAVIES PTG, STEINER TJ: Serotonin S2 receptors and migraine: a study with the selective antagonist ICI 169,369. *Headache* (1990) 30:340-343.
Modest antimigraine effect of a 5-HT$_{1C/2}$ receptor antagonist in a clinical trial.

250. BLACKBURN TP, THORNBER CW, PEARCE RJ, COX B: In vitro studies with ICI 169,369, a chemically novel 5-HT antagonist. *Eur. J. Pharmacol.* (1988) 150:247-256.

251. COUCH JR, HASSENEIN RS: Amytryptaline in migraine prophylaxis. *Arch. Neurol.* (1979) 36:695-699.

252. MARKELY HG, GASSER PA, MARKLEY ME, PRATT SM: Fluoxetine in prophylaxis of headache: Clinical experience. *Cephalagia.* (1991) 11:S11.

253. ADLEY C, STRAUMANIS J, CHESSON A: Fluoxetine prophylaxis of migraine. *Headache* (1992) 32:101-104.

254. GRIFFITHS WJ, LESTER BK, COULTER JD, WILLIAMS HL: Tryptophan and sleep in young adults. *Psychophysiology* (1972) 9:245-356.

255. HARTMANN E, CRAVENS J, LIST S: Hypnotic effects of 1-tryptophan. *Arch. Gen. Psychiatry* (1974) 31:394-397.

256. MENDELSON WB, GILLIN JC, WYATT RJ: Human sleep and its disorders. Plenum, New York, (1977) pp 21-62.

257. JOUVET M: The role of monoamines and acetyl-containing neurons in the regulation of the sleep-waking cycle. *Erg. Physiol. Biol. Chem. Exp. Pharmakol.* (1972) 64:166-307.

258. WYATT RJ: The serotonin-catecholamine dream bicycle: a clinical study. *Biol. Psychol.* (1972) 5:33-63.

259. KAFI-DE ST HILAIRE S, HJORTH S, GAILLARD JM: Brain 5-HT$_{1A}$ receptors: Behavioural and neurochemical pharmacology. Dourish CT, Ahlenius S, Hutson PH, (Eds): Ellis Horwood Ltd, Chichester, U.K. (1987):135-139.

260. DZOLJIC MR, SAXENA PR, UKPONMWAN OE: Activation of "5-HT$_1$- like" receptors stimulates wakefulness. *Brit. J. Pharmacol.* (1986) 89:522P.

261. SEIDEL WF, COHEN SA, BLIWISE NG, DEMENT WC: Buspirone, an anxiolytic without sedative properties. *Psychopharmacology* (1985) 87:371-373.

262. LAWLOR BA, NEWHOUSE PA, BALKIN TJ, MOLCHAN SE, MELLOW AM, MURPHY DL, SUNDERLAND T: A preliminary study of the effects of nighttime administration of the serotonin agonist, m-CPP, on sleep architecture and behaviour in healthy volunteers. *Biol. Psychiat.* (1991) 29:281-286.
First study revealing sleep disruption after mCPP.

263. SHARPLEY AL, KATSUDA Y, WARE CJG, WALSH AES, COWEN PJ: The effect of mCPP on sleep in healthy volunteers. *J. Psychopharmacol* (1992) Abstr BAP/EPBS meeting, A7.

264. NICHOLSON AN, PASCO PA: 5-Hydroxytryptamine and noradrenergic uptake inhibition: Studies on sleep in man. *Neuropharmacology* (1986) 256:1079-1083.

265. DUGOVIC C, WAUQUIER A: 5-HT$_2$ receptors could be primarily involved in the regulation of slow-wave sleep in the rat. *Eur. J. Pharmacol.* (1987) 137:145-146.
A 5-HT$_{1C/2}$ receptor antagonist was observed to increase slow wave, but decrease rapid eye movement in this rat sudy.

266. BJORVATN B, URSIN R: Effects of Zimeldine, a selective 5-HT reuptake inhibitor, combined with ritanserin, a selective 5-HT$_2$ antagonist, on waking and sleep stages in rats. *Behav. Brain Res.* (1990) 40:239-246.

267. PASTEL RH, FERNSTROM JD: Short-term effects of fluoxetine and trifluoromethylphenyl-piperazine on electroencephalographic sleep in the rat. *Brain Res.* (1987) 436:92-102.

268. KAFI-DE ST HILAIRE S, MERCIA H, GAILLARD JM: The effects of indalpine - a selective inhibitor of 5-HT uptake - on rat paradoxical sleep. *Eur. J. Pharmacol.* (1984) 98:413-418.

269. SOMMERFELT L, HAUGE ER, URSIN R: Similar effects on REM sleep but differential effect on slow

wave sleep of the 5-HT uptake inhibitors zimeldine and alaproclate in cats and rats. *J. Neural Trans.* (1987) 68:127-144.

270. HILAKIVI I, KOVALA T, LEPPAVUORI A, SHVALOFF A: Effects of serotonin and noradrenaline uptake blockers on wakefulness and sleep in cats. *Pharmacol. Toxicol.* (1987) 60:161-166.

271. CLARENBACH P, BIRMANNS B, KRATZSCHMAR S, JAURSCH-HANCKE C: Sleep pattern and nocturnal plasma profiles of HGH, prolactin and cortisol in man after the serotonin-antagonist ritanserin and the GABA-agonist gabapentin. *Sleep Res.* (1986) 15:29.

272. IDZIKOWSKI C, MILLS FJ, GLENNARD R: 5-
• Hydroxytryptamine-2-antagonist increases human slow wave sleep. *Brain Res.* (1986, 378:164-168.
Slow wave sleep enhancing and rapid eye movement sleep inhibiting effects of a 5-HT$_{1C/2}$ receptor antagonist observed in this clinical study.

273. IDZIKOWSKI C, COWN PJ, NUTT D, MILLS FJ: The effects of chronic ritanserin treatment on sleep and the neuroendocrine response to l-tryptophan. *Psychopharmacology* (1987) 93:416-420.

274. DECLERCK AC, WAUQUIER A, VAN DER HAM-VELTMAN PHM, GELDERS Y: Increase in slow-wave sleep in humans with the serotonin-S2 antagonist ritanserin. *Curr. Therap. Res.* (1987) 41:427-432.

275. ADAM K, OSWALD I: Effects of repeated ritanserin on middle- aged poor sleepers. *Psychophar- macology* (1989) 99:219-221.

276. IDZIKOWSKI C, MILLS FJ, JAMES RJ: A dose-response study examining the effects of ritanserin on human slow wave sleep. *Brit. J. Clin. Pharmacol.* (1991) 31:193-196.

277. PAIVA T, WAUQUIER A, LARA E, LARGO R, LEITANO JN: Effects of ritanserin on sleep disturbances of dysthymic patients. *Psychopharmacology* (1988) 96:395-399.

278. RUIZ-PRIMO E, HARO R, VALENCIA M: Polysomnographic effects of ritanserin in insomniacs in a crossed double-blind controlled study. *Sleep Res.* (1989) 18:72.

279. DAHLITZ M, WELLS P, JAMES R, IDZIKOWSKI C, PARKES JD: Treatment of insomnia with ritanserin. *Lancet* (1990) 336:379.

280. TORMEY WP, BUCKLEY MP, O'KELLY DA, CONBOY J, PINDER RM, DARRAGH MD: Sleep-endocrine profile of the antidepressant mianserin. *Curr. Med. Res. Opinion* (1980) 6:456-460.

281. GENCO S, PUCA FM, SPECCHIO LM, INTERNO S, CASTRIOTTA R, LEOMANNI R, DAMMACCO F: Metergolina e sonno notturno nell, uomo normale. *Boll. Soc. Ital. Biol. Sper.* (1977) 53:1403-1406.

282. SOLOMON RA, SHARPLEY AL, COWEN PJ: Increased slow-wave sleep with 5-HT$_2$ receptor antagonists: Detection by ambulatory ECG recording and automatic sleep stage analysis. *J.*

Pharmacol. (1989) 3:125-129.

283. SPIEGEL R: Sleep 1980. 5th European congress on sleep research. Koella WP, (Ed): Karger, Basel, (1981), pp 275-278.

284. MENDELSON WB, JACOBS LS, REICHMAN JD, OTHMER E, CRYER PE, TRIVEDI B, DAUGHADAY WH: Methysergide: suppression of sleep related prolactin excretion and enhancement of sleep related growth hormone secretion. *J. Clin. Invest.* (1975) 56:690-697.

285. DUGOVIC C, WAUQUIER A, LEYSEN JE, MARRANNES R, JANSSEN PAJ: Functional role of 5-HT$_2$ receptors in the regulation of sleep and wakefulness in the rat. *Psychopharmacology* (1989) 97:436-442.

286. TORTELLA FC, ECHEVARRIA E, PASTEL RH, COX B, BLACKBURN TP: Suppressant effects of selective 5-HT$_2$ antagonists on rapid eye movement sleep in rats. *Brain Res.* (1989) 485:294-300.

287. DAVENNE D, DUGOVIC C, FRANC B, ADRIEN J: Slow wave sleep: Physiological, pathophysiological and functional aspects. Raven Press, New York, (1989), pp 21-30.

288. NEIL JC, COOPER SJ: Evidence that d-fenfluramine anorexia is mediated by 5-HT$_1$ receptors. *Psychopharmacology* (1989) 97:213- 218.

289. HUTSON PH, DONOHOE TP, CURZON G: Infusion of
• the 5- hydroxytryptamine agonists RU 24969 and TFMPP into the paraventricular nucleus of the hypothalamus causes hypophagia. *Psychopharmacology* (1988) 95:550-552.
Evidence that 5-HT$_{1C}$-mediated hypophagia in rats may be mediated by the paraventricular nucleus of the hypothalmus.

290. KENNETT GA, CURZON G: The antiemetic trimethobenzamide prevents hypophagia due to acetyl salicylate, but not to 5-HT$_{1B}$ or 5-HT$_{1C}$ agonists. *Psychopharmacology* (1988) 96:101-103.

291. CLINESCHMIDT BV, McGUFFIN JC, PFEUGER AB, TOTARO JA: A 5- hydroxytryptamine-like mode of anorectic action for 6-chloro-2-(1-piperazinyl)-pyrazine (MK 212). *Brit. J. Pharmacol.* (1978) 62:579-589.

292. SCHECHTER LE, SIMANSKY KT: 1-(2,5-dimethoxy-4-iodophenyl)-2- aminopropane (DOI) exerts an anorexic action that is blocked by 5-HT$_2$ antagonists in rats. *Psychopharmacology* (1988) 94:342-346.

293. HEWSON G, LEIGHTON GE, HILL RG, HUGHES J: Quipazine induces food intake in the rat by activation of 5-HT$_2$ receptors. *Brit. J. Pharmacol.* (1989) 95:598-604.

294. WILKINSON LO, DOURISH CT: Serotonin receptor subtypes: Basic and clinical aspects. Wiley-Liss, inc., (1991), pp 147-210.

295. DOURISH CT, CLARK ML, FLETCHER A, IVERSEN SD: Evidence that blockade of postsynaptic 5-HT$_1$ receptors elicits feeding in satiated rats. *Psychopharmacology* (1989) 97:54-58.

296. FLETCHER PJ: Increased food intake in satiated rats induced by the 5-HT antagonists

methysergide, metergoline and ritanserin. *Psychopharmacology* (1988) 96:237-242.

297. MASSI M, MARINI S: Effects of the 5-HT$_2$ antagonist ritanserin on food intake and on 5-HT-induced anorexia in the rat. *Pharmacol. Biochem. Behav.* (1987) 26:333-340.

298. BAXTER MJ, MILLER AA, SOROKO FE: The effect of cyproheptadine on food consumption in the fasted rat. *Brit. J. Pharmacol.* (1970) 39:229-230.

299. GHOSH MN, PARVATHY S: The effect of cyproheptadine on water and food intake and on body weight in the fasted adult and weanling rats. *Brit. J. Pharmacol.* (1973) 48:328-329.

300. SWIERGIEL AH, PETERS G: Failure of serotonin antagonist pizotifen to stimulate feeding or weight gain in free-feeding rats. *Pharmacol. Biochem. Behav.* (1990) 35:61-67.

301. LAVENSTEIN AF, LASAGNA L, VAN METRE TE: Effect of
• cyproheptadine on asthmatic children, study of appetite, weight gain and linear growth. *JAMA* (1962)180:912-916.
Hyperphagic effects of a putative 5-HT$_{1C/2}$ receptor antagonist in man reported.

302. BERGEN SS: Appetite stimulating properties of cyproheptadine. *Am. J. Dis. Child.* (1964) 108:270-273.

303. KAHN RS, WETZLER S: m-Chlorophenylpiperazine as a probe of serotonin function. *Bioll Psychiat.* (1991) 30:1139-1166.

304. ROWLAND NE, CARLTON J: Neurobiology of an anorectic drug: Fenfluramine. *Prog. in Neurobiol.* (1986) 27:13-62.

305. HEWSON G, LEIGHTON GE, HILL RG, HUGHES J: Ketanserin antagonises the anorectic effect of DL-fenfluramine in the rat. *Eur. J. Pharmacol.* (1988) 145:227-230.

306. GARATTINI S, MENNINI T, BENDOTTI C, INVERNIZZI R, SAMANIN R: Neurochemical mechanism of action of drugs which modify feeding via the serotonergic system. *Appetite* (1986) 7 (Suppl):15-38.

307. GIBSON EL, KENNEDY AJ, CURZON G: D-
• fenfluramine and D-norfenfluramine hypo-
.. phagia: involvement of postsynaptic 5-HT$_{1C}$ receptors? *J. Psychopharmacol.* (1992) Abstr. BAP/EPBS Meeting: A83.
Fenfluramine-induced hypophagia in rats concluded to be 5-HT$_{1C}$ receptor-mediated in this study.

308. ORZACK MH, FRIEDMAN LM, MARBY DW: Weight changes on fluoxetine as a function of baseline weight in depressed outpatients. *Psychopharmacology Bull.* (1990) 26:327-330.

309. RASMUSSEN JGC, JOHNSTON AM, STEWART B, PALMER KJ: Comparative effects of the selective serotonergic uptake inhibitors paroxetine and fluoxetine on food intake in rats and effect of paroxetine on body/weight in depressed patients. *J. Psychopharmacol.* (1990) 4:300.

310. ROWLAND N, ANTELMAN SM, KOCAN D: Differences among serotonergic anorectics in a cross-tolerance paradigm: Do they act on serotonin systems? *Eur. J. Pharmacol.* (1982) 81:57-66.

311. GOUDIE AJ, THORNTON EW, WHEELER TJ: Effect of Lilly 110140, a specific inhibitor of 5-hydroxytryptamine uptake on food intake and on 5-hydroxytryptophan-induced anorexia. Evidence for serotonergic inhibition of feeding. *J. Pharm. Pharmacol.* (1976) 28:318-320.

312. LEANDER JD: Fluoxetine suppressed palatability-induced ingestion. *Psychopharmacology* (1987) 91:285-287.

313. GILL K, AMIT ZA: Effects of serotonin uptake blockade on food water and ethanol consumption in rats. *Alcoholism: Clin. Exp. Res.* (1987) 11:444-449.

314. DUMONT C, LAURENT J, GRANDADAM A, BOISSIER JR: Anorectic properties of a new long acting serotonin uptake inhibitor. *Life Sci.* (1981) 28:1939-1945.

315. LUCKI K, KREIDER MS, SIMANSKY KJ: Reduction of feeding behaviour by the serotonin uptake inhibitor sertraline. *Psychopharmacology* (1988) 96:289-295.

316. NIELSEN JA, CHAPIN DS, JOHNSON JL, TORGERSEN LK: Sertraline, a serotonin-uptake inhibitor, reduces food intake and body weight in lean rats and genetically obese mice. *Am. J. Clin. Nutr.* (1992) 55:185S-188S.

317. WONG DT, REID LR, THRELKELD PG: Suppression of food intake by fluoxetine: comparison of enantiomers and effects of serotonin antagonists. *Pharmacol. Biochem. Behav.* (1988) 31:475-479.

318. WEISS GF, PAPADAKOS P, KNUDSON K, LEIBOWITZ SF: Medial hypothalamic serotonin: Effects on deprivation and norepinephrine-induced eating. *Pharmacol. Biochem. Behav.* (1986) 25:1223-1230.

319. FLETCHER PJ, BURTON MJ: Dissociation of the anorectic actions of 5-HTP and fenfluramine. *Psychopharmacology* (1986) 89:216-220.

320. BAKER BJ, DUGGAN JP, BARBER DJ, BOOTH DA: Effects of dl-fenfluramine and xylamidine on gastric emptying of maintenance diet in freely feeding rats. *Eur. J. Pharmacol.* (1988) 150:137-142.

321. FERGUSON JM, FEIGHNER JP: Fluoxetine-induced weight loss in overweight nondepressed humans. *Int. J. Obesity* (1987) 11 (Suppl):179S-184S.

322. LEVINE LR, ROSENBLATT S, BOSOMWORTH JC: Use of serotonin reuptake inhibitor, fluoxetine in the treatment of obesity. *Int. J. Obesity* (1987) 11 (suppl):185S-190S.

323. LEVINE LR, ENAS GG, THOMPSON WL, BYYNY RL, DAUER AD, KIRBY RW, KREINDLER TG, LEVY B, LUCAS CP, MCILWAIN HH, NELSON EB: Use of fluoxetine, a selective serotonin-uptake inhibitor in the treatment of obesity: a dose-response study. *Int.*

J. Obesity (1989) 13:635-645.

324. ROBINSON PH, CHECKLEY SA, RUSSELL GFM: **Suppression of eating by fenfluramine in patients with Bulimia Nervosa.** *Brit. J. Psychiat.* (1985) 146:169-176.

325. BLOUIN AG, BLOUIN JH, PEREZ EL, BUSHNIK T, ZURO C: **Treatment of bulimia with fenfluramine and desipramine.** *J. Clin. Psychopharmacol.* (1988) 8:261-269.

326. WALSH BT, GLADIS M, ROOSE SP, STEWART JW, STETNER F, GLASSMAN AH: **Phenelzine vs placebo in 50 patients with bulimia.** *Arch. Gen. Psychiat.* (1988) 45:471-475.

327. KENNEDY SH, PIRAN N, WALSH JJ, PRENDERGAST P, MAINPRIZE E, SHYNOT C, GARFINKEL PE: **A trial of isocarboxazid in the treatment of bulimia nervosa.** *J. Clin. Psychopharmacol.* (1988) 8:391-396.

328. FREEMAN CPL, HAMPSON M: **Fluoxetine as a treatment for bulimia nervosa.** *Int. J. Obesity* (1987) 11 (suppl 3):171-177.

329. POPE HG, KECK PE, McELROY SM, HUDSON JL: **A placebo-controlled study of trazodone in bulimia nervosa.** *J. Clin. Psychopharmacol.* (1989) 9:254-259.

330. GOLDBLOOM DS, KENNEDY SH: **Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa.** *J. Clin. Psychiat.* (1991) 52:261-262.

331. BARLOW J, BLOUIN J, BLOUIN A, PEREZ E: **Treatment of bulimia with desipramine: a double-blind crossover study.** *Can. J. Psychiat.* (1988) 33:129-133.

332. HUGHES PL, WELLS LA, CUNNINGHAM CJ, ILSTRUP DM: **Treating bulimia with desipramine: a placebo-controlled double-blind study.** *Arch. Gen. Psychiat.* (1986) 43:182-186.

333. PRICE WA, BABAI MR: **Antidepressant drug therapy for bulimia: Current status revisited.** *J. Clin. Psychiat.* (1987) 48:385.

334. SABINE EJ, YONACE A, FARRINGTON AJ, BARRAT KH, WAKELING A: **Bulimia nervosa: a placebo-controlled double-blind therapeutic trial of mianserin.** *Brit. J. Clin. Pharmacol.* (1983) 15 (suppl):195S-202S.

335. NOBLE RE: **Effect of cyproheptadine on appetite and weight gain in adults.** *JAMA* (1969) 209:2054-2055.

336. SILVERSTONE T, SCHUYLER D: **The effect of cyproheptadine on hunger, calorie intake and body weight in man.** *Pychopharmacologia* (1975) 40:335-340.

337. GLOBISCH J: **Appetitlosigkeit, nervositat und untergewicht.** *Arztl. Praxis* (1979) 29:1877-1881.

338. JENSCHKE H: **Zur behandlung von appetitosigkeit und untergewicht bei alterspatienten.** *Therapiewoche* (1979) 29:1877-1881.

339. MARTINDALE: **The extra pharmacopoeia.** 29th edition. Reynolds JR (ed). The Pharmaceutical Press, London, (1989).

340. GOLDBERG SC, HALMI KA, ECKERT ED, CASPER R, DAVIS JM: **Cyproheptadine in anorexia nervosa.** *Brit. J. Psychiat.* (1979) 134:67-70.
• Failure of a putative 5-HT$_{1C/2}$ receptor antagonist and appetite enhancer to exhibit clinical efficacy in anorexia nervosa.

341. VIGERSKY RA, LORIAUX DL: **Anorexia nervosa.** Vigersky R (ed). Raven Press, New York, (1977), pp143-161.

342. HALMI KA, ECKERT E, LA DU TJ, COHEN J: **Anorexia nervosa: treatment efficacy of cyproheptadine and amitryptyline.** *Arch. Gen. Psychiat.* (1986) 43:177-181.

343. CRISP AH, LACEY JH, CRUTCHFIELD M: **Clomipramine and "drive" in people with anorexia nervosa: an inpatient study.** *Brit. J. Psychiat.* (1987) 150:355-358.

344. McENTEE WJ, COOK TH: **Serotonin, memory, and the aging brain.** *Psychopharmacology* (1991) 103:143-149.

345. ALTMAN HJ, NORDY DA, OGREN SO: **Role of serotonin in memory: Facilitation by alaproclate and zimeldine.** *Psychopharmacology* (1984) 84:496-502.

346. FLOOD JF, CHERKIN A: **Fluoxetine enhances memory processing in mice.** *Psychopharmacology* (1987) 93:36-43.

347. STREK KI, SPENCER KR, DeNOBLE VJ: **Manipulation of serotonin protects against an hypoxia-induced deficit of a passive avoidance response in rats.** *Pharmacol. Biochem. Behav.* (1989) 33:241-244.

348. ALTMAN HJ, STONE WS, OGREN SO: **Evidence for a possible functional interaction between serotonergic and cholinergic mechanisms in memory retrieval.** *Behav. Neural. Biol.* (1987) 48:49-62.

349. NYETH A-L, BALLADIN J, ELGEN K, *et al.*: **Behandling Med citalopram vid demens. Normalisering av DST.** *Nordic Psykiatrisk Tidskrift* (1987) 41:423-430.

350. NYETH A-L, GOTTFRIES CG: **The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A nordic multicentre study.** *Br. J. Psychiat.* (1990) 157:894-901.

351. FUDGE JL, PERRY PJ, GARVEY MJ, KELLY MW: **A comparison of the effect of fluoxetine and trazodone on the cognitive functioning of depressed patient.** *J. Affective Disord.* (1990) 18:275-280.

352. MOSKOWITZ H, BURNS M: **The effects on performance of two antidepressant, alone and in combination with diazepam.** *Prog. Neuropsychopharmacol. Bio. Psychiat.* (1988) 12:783-792.

353. NICHOLSON AN, PASCOE PA: **Studies on the modulation of the sleep-wakefulness**

continuum in man by fluoxetine, a 5-HT uptake inhibitor. *Neuropharmacology* (1988) 27:597-602.

354. WEINGARTNER H, RUDORFER MV, BUCHSBAUM MS, LINNOILA M: **Effects of serotonin on memory impairments produced by ethanol.** *Science* (1983) 221:472-474.

355. MARTIN PR, ADINOFF B, ECKARDT MJ, STAPLETON JM, BONE GAH, RUBINOW DR, LANE EA, LINNOILA M: **Effective pharmacotherapy of alcoholic amnesic disorder with fluvoxamine.** *Arch. Gen. Psychiat.* (1989) 46:617-621.

356. ECKHARDT MJ, STAPLETON JM, RIO D, GEORGE DT, RAWLINGS RR, WEINGARTNER H, LINNOILA M: **Interactions of fluvoxamine and ethanol in healthy volunteers.** 15th Collegium Int. Neuro-psychopharmacologium (1986) pp 55-57.

357. SALETU B, GRUNBERG J, RAJNA P, KAROBATH M: **Clovoxamine and fluvoxamine: 2 biogenic amine reuptake inhibiting antidepressants: quantitative EEG, psychometric and pharmacokinetic studies in man.** *J. Neural Transm.* (1980) 49:63-86.

358. CURRAN HV, LADER M: **The psychopharmacological effects of repeated doses of fluvoxamine, mianserin and placebo in healthy human subjects.** *Eur. J. Clin. Pharmacol.* (1986) 29:601-607.

359. BARTFAI A, ASBERG M, MARTENSSON B, GUSTAVSSON P: **Memory effect of clomipramine treatment: Relationship to CSF monoamine metabolites and drug concentrations in plasma.** *Biol. Psychiat.* (1991) 30:1075-1092.

360. HINDMARCH I, BHATTI JZ: **Psychopharmacological effects of sertraline in normal, healthy volunteers.** *Eur. J. Clin. Pharmacol.* (1988) 35:221-223.

361. CURRAN HV, SHINE P, LADER M: **Effects of repeated doses of fluvoxamine, mianserin and placebo on memory and measures of sedation.** *Psychopharmacology* (1986) 89:360-363.

362. HINDMARCH I, SHILLINGFORD J, SHILLINGFORD C: **The effects of sertraline on psychomotor performance in elderly volunteers.** *J. Clin. Psychiat.* (1990) 51:12 (suppl B):34-36.

363. ALTMAN HJ, NORMILE HJ: **Enhancement of the memory of a previously learned aversion habit following pre-test administration of a variety of serotonergic antagonists in mice.** *Psychopharmacology* (1986) 90:24-27.

364. NORMILE HJ, ALTMAN HJ: **Enhanced passive avoidance retention following poststrain serotonergic receptor antagonist administration in middle-aged and aged rats.** *Neurobiol. Aging* (1988) 9:377-382.

365. HAKKOU F, JAOUNEN C, IRAKI L: **A comparative study of cyproheptadine and DL carnithine on psychomotor performance and memory in healthy volunteers.** *Fundam. Clin. Pharmacol.* (1990) 4:191-200.

366. SEIBYL JP, KRYSTAL JH, PRICE LH, WOODS SW,
•• HENINGER GR, CHARNEY DS: **5-HT function in the biochemical and behavioural responses to mCPP in healthy subjects and schizophrenics.** *Am. Soc. Neurosci. Abstr.* (1989) 15:485.21.
First report that mCPP can induce psychosis in scizophrenics.

367. KRYSTAL JH, SEIBYL JP, PRICE LP, WOODS SWM. HENINGER GR, CHARNEY DS: **MCPP effect in schizophrenic patients before and after typical and atypical neuroleptic treatment.** *Schizophrenia Res.* (1991) 4:350.

368. IQBAL N, ASNIS GM, WETZLER S, KAHN RS, KAY S, VAN PRAAG HM: **The mCPP challenge test in schizophrenia: Hormonal and behavioural responses.** *Bio. Psychiat.* (1991) 30:770-778.

369. OWEN RR, GUTIERREZ L, HADD K, BENKELFAT C, MURPHY DL: **Serotonergic responsivity in schizophrenia.** *Am Psychiat. Assoc.* (1990) New Res Abstr: NR235.

370. KAHN RS, SIEVER LJ, GABRIEL S, AMIN F, STERN RG, DUMONT K, APTER S, DAVIDSON M: **Serotonin function in schizophrenia: Effects of metachlorophenylpiperazine in schizophrenic patients and healthy subjects.** *Psychiatry Res.* (1992) 43:1-12.

371. GELDERS Y, VAN DEN BUSSCHE G, REYNTJENS A, JANSSEN P: **Serotonin S2 receptor blockers in the treatment of chronic schizophrenia.** *Clin. Neuropharmacol.* (1986) 9:325-327.

372. GELDERS YG: **Thymosthenic agents, a novel approach in the treatment of schizophrenia.** *Brit. J. Psychiat.* (1989) 155 (suppl. 5):33-36.

373. SILVER H, BLACKER M, WELLER MPI, LERER B: **Treatment of chronic schizophrenia with cyproheptadine.** *Biol. Psychiat.* (1989) 25:502-504.

374. BERSANI G, GRISPINI A, PASINI MA, VALDUCCI M, CIANI N: **5-HT₂ antagonist ritanserin in neuroleptic-induced parkinsonism: a double-blind comparison with orphenadrine and placebo.** *Clin. Neuropharmacol.* (1990) 13:500-506.

375. MAERTENS DE NOORDHOUT A, DELWAIDE PJ: **Open pilot trial of ritanserin in Parkinson's disease.** *Curr. Therap. Res.* (1986) 9:480-484.

376. MECO G, MARINI S, LESTING L, L'INFANTE I, MODARELLI F, AGNOLI A: **Controlled single-blind cross-over study of ritanserin and placebo in l-DOPA-induced dyskinesias in Parkinson's disease.** *Curr. Therap. Res.* (1988) 43:262-270.

377. MILLER CH, FLEISHACKER WW, EHRMANN H, KANE JM: **Treatment of neuroleptic induced akathisia with the 5-HT₂ antagonist ritanserin.** *Psychopharmacol. Bull.* (1990) 26:373-376.

378. MELTZER HY: **Clinical studies on the mechanism
•• of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia.** *Psychopharmacology* (1989) 99:S18-S27.
Proposal that 5-HT₂ receptor antagonist efficacy was

important to the improved profile of atypical antipsychotic drugs.

379. CANTON H, VERRIELE L, COLPAERT FC: **Binding of typical and atypical antipsychotics to 5-HT$_{1C}$ and 5-HT$_2$ sites: clozapine potently interacts with 5-HT$_{1C}$ sites.** *Eur. J. Pharmacol.* (1990) 191:93-96.
Proposal that 5-HT$_{1C}$ receptors may mediate the improved side effect profile and efficacy against negative symptoms of 'atypical' antipsychotic drugs.

380. ROTH BL, CIARANELLO RD, MELTZER HY: **Binding of typical and atypical antipsychotic agents to transiently expressed 5-HT$_{1C}$ receptors.** *J. Pharmacol. Exp. Therap.* (1990) 260:1361-1365.
Refutation of the hypothesis that 5-HT$_{1C}$ receptors mediate the improved side effect profile and efficacy against negative symptoms of atypical antipsychotic drugs.

381. CEULEMANS DLS, GELDERS YG, HOPPENBROUWERS M-L, et al.: **Effect of serotonin antagonism in schizophrenia: a pilot study with setoperone.** *Psychopharmacology* (1985) 85:329-332.

382. HARNRYD C, BJERNSTADT L, GULLBERG B: **A clinical comparison of melperone and placebo in schizophrenic women on a milieu therapeutic ward.** *Acta. Psych. Scand. Suppl.* (1989) 352:40-47.

383. CHRISTENSSON EG: **Pharmacological data of the atypical neuroleptic compounds melperone.** *Acta. Psychiat. Scand. Suppl.* (1989) 352:7-15.

384. GUNNE LM, JOHANSSON P: **Chronic melperone administration does not induce oral movements in rats.** *Acta. Psychiat. Scand. Suppl.* (1989) 352:48-50.

385. SVARTENGREN J, SIMONSSON P: **Receptor binding properties of amperozide.** *Pharmacol. Toxicol.* (1990) 66 (suppl 1):11.

386. ALBINSSON A, ERIKSSON E, ANDERSSON G: **Amperozide-effect on prolactin release in the rat.** *Pharmacol. Toxicol.* (1990) 66 (suppl 1):49-51.

387. CHRISTENSSON EG, BJORK A: **Amperozide: a new pharmacological approach in the treatment of schizophrenia.** *Pharmacol. Toxicol.* (1990) 66 (suppl 1):5-7.

388. ANDERSON GM, HORNE WC, CHATTERJEE D, COHEN DJ: **The hyperserotonemia of autism.** *Ann. N. Y. Acad. Sci.* (1990) 600:331- 340.

389. CLINESCHIDT BV, ZACCHEI AG, LOTARO JA, PFLUEGER AB, McGUFFIN JC, WISHOUSKY TI: **Fenfluramine and brain serotonin.** *Ann. N. Y. Acad. Sci.* (1978) 305:222-241.

390. GELLERE E, RITVO ER, FREEMAN BJ, YUWILER A: **Preliminary observations on the effect of fenfluramine on blood serotonin and symptoms in three autistic boys.** *N. Engl. J. Med.* (1982) 307:165- 169.

391. AMAN MG, KERN RA: **Review of fenfluramine in the treatment of the developmental disabilities.** *J. Am. Acad. Child Adolesc. Psychiat.* (1989) 28:549-565.

392. FISH B, CAMPBELL M, SHAPIRO T, FLOYD A: **Schizophrenic children treated with**

393. PRANZATELLI MR, MURTHY JN, PLUCHINO RS: **Identification of spinal 5-HT$_{1C}$ binding sites in the rat: characterization of [^{3}H]mesulergine binding.** *J. Pharm. Exp. Ther.* (1992) 261:161-165.

394. HARRIS GD, ZEMLAN FP, MURPHY RM, BEHBEHANI MM: **Spinal cord 5-HT, 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes: relation to pain transmission** *neurosci.* Abstr. (1986) 12:1015.

395. ZEMLAN FP, BEHBEHANI MM, MURPHY RM: **Serotonin receptor subtypes and the modulation of pain transmission.** *Prog. in Brain Res.* (1988) 77:349-355.

396. McKEARNEY JW: **Apparent antinociceptive properties of piperazine-type serotonin agonists: Trifluoromethylphenylpiperazine, chlorophenylpiperazine, and MK-21.** *Pharmacol. Biochem. Behav.* (1989) 32:657-660.

397. SANDRINI G, ALFONSO E, DE RYSKY C , MARINI S, FACCHINETTI F, NAPPI G: **Evidence for serotonin-S2 receptor involvement in analgesia in humans.** *Eur. J. Pharmacol.* (1986) 130:311-314.

398. SZELE FG, MURPHY DL, GARRICK NA: **Effects of fenfuramine, m- chlorophenylpiperazine, and other serotonin-related agonists and antagonists on penile erections in non human primates.** *Life Sci.* (1988) 43:1297-1303.
MCPP observed to cause penile erection in primates.

399. BARALDI M, BENASSI-BENELLI A, LOLLI M: **Penile erections in rats after fenfluramine administration.** *Riv. Farmacol. Ther.* (1977) 8:375-379.

400. BERENDSEN HHG, BROEKKAMP CLE: **Drug-induced penile erections in rats: indications of serotonin 1B receptor mediation.** *Eur. J. Pharmacol.* (1987) 135:279-287.

401. KRANE RJ, GOLDSTEIN I, SAENZ DE TEJADA I: **Impotence.** *N. Engl. J. Med.* (1989) 321:1648-1649.

402. BAHOS JE, BOSCH F, FARRE M: **Drug-induced priapism. Its aetiology, incidence and treatment.** *Med. Toxicol. Adverse Drug Exper.* (1989) 4:46-58.

403. CSERR HF: **Physiology of the choroid plexus.** *Physiol. Rev.* (1971) 51:273-311.

404. DAVSON H, WELCH K, SEGAL MB: **The physiology and pathophysiology of the cerebrospinal fluid.** Churchill Livingstsone, New York (1987).

405. LINDVALL-AXELSSON M, MATHEW C, NILSSON C, OWMAN C: **Effect of 5-hydroxytryptamine on the rate of cerebrospinal fluid production in rabbit.** *Exp. Neurol.* (1988) 90:362-268.

406. MAEDA K: **Monoaminergic effects on cerebrospinal fluid production.** *Nihon Univ. J. Med.* (1983) 25:155-174.

407. VAN NUETEN JM, JANSSENS WJ, VANHOUTTE PM: **Serotonin and vascular smooth muscle.** Vanhoutte PM (Ed). Raven Press, New York (1985).

methysergide (Sansert). *Dis. Nerv. Syst.* (1969) 30:534-540.

408. DROPP JJ: Mast cells in the central nevous system of several rodents. *Anat. Rec.* (1972) 174:227-233.

409. EDVINSSON L, LINDVALL M: Autonomic vascular innervation and vasomotor reactivity in the choroid plexus. *Exp. Neurol.* (1978) 62:394-404.

410. MOSKOWITZ MA, LIEBMANN JE, REINHARD JF, SCHLOSBERG A: Raphe origin of serotonin-containing neurons within the choroid plexus of the rat. *Brain Res.* (1979) 169:590-594.

411. NAPOLEONE P, SANCESARIO G, AMENTA F: Indoleaminergic innervation of rat choroid plexus: a fluorescence histochemical study. *Neurosci. Lett.* (1982) 34:143-147.

412. LOREZ HP, RICHARDS JG: 5-HT nerve terminals in the fourth ventricle of the rat brain: their identification and distribution studied by fluorescence microscopy. *Cell Tissue Res.* (1975) 165:37-34.

413. MATSUURA T, TAKEUCHI Y, KOJIMA M, UEDA S, YAMADA H, NOJYO Y, USHIJIMA K, SANO Y: Immunohistochemical studies of the serotonergic supraependymal plexus in the mammalian ventricular system, with special reference to the characteristic reticular ramification. *Acta Anat.* (1985) 123:207-219.

414. SKARSFELDT T, LARSEN JJ: SCH 34490 - a selective dopamine D_1 receptor antagonist with putative 5-HT$_1$ receptor agonistic activity. *Eur. J. Pharmacol.* (1988) 148:389-395.

415. BOYSON SJ, McGONIGLE P, MOLINOFF PB: Quantitative autoradiographic localisation of the D_1 and D_2 subtypes of dopamine in the rat brain. *J. Neurosci.* (1986) 6:3177-3188.

416. BOYSON SJ, ALEXANDER A: Net production of cerebrospinal fluid is decreased by SCH-34490. *Ann. Neurol.* (1990) 27:631-635.

417. TURCONI M, SCHIANTARELLI P, BORSINI F, RIZZI CA, LADINSKY H, DONETTI A: Azabicycloalkyl benzimidazolones: interaction with serotonergic 5-HT$_3$ and 5-HT$_4$ receptors and potential therapeutic implications. *Drugs of the Future* (1991) 16:1011-1026.

418. CARR AA, HAY DA, DUDLEY MW, NIEDUZAK TR:
• Derivatives of MDL 11939 as highly potent and selective inhibitors of serotonin 5-HT$_2$ receptors. Abstract 180, *The Second IUPHAR Satellite Meeting on Serotonin.* Basel, Switzerland, July 1990. Abs 180
Report of the development of very selective 5-HT$_2$ receptor antagonists.

419. COHEN ML, WITTENAUER LA: Further evidence that the serotonin receptor in the rat stomach fundus is not 5-HT$_{1A}$ or 5-HT$_{1B}$. *Life Sci.* (1986) 38:1-5.

420. TEICHER MH, GLOD C, COLE JO: Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am. J. Psychiat.* (1990) 147:207-210.

421. LEBEGUE BJ: Sudden self harm while taking fluoxetine. *Am. J. Psychiat.* (1992) 149:1113.

422. DOWNS J, WARD J, FARMER R: Preoccupation with suicide in patients treated with fluoxetine. *Am. J. Psychiat.* (1991) 148:1090-1092.

423. HOYER D, FOZARD JR: Receptor data for biological experiments: a guide to drug selectivity. Doods HN, Van Meel JCA, (Eds). Ellis Horwood series in biological sciences, New York, (1991), pp 35-41.

424. HOYER D: Functional correlates of serotonin 5-HT1 recognition sites. *J. Recept. Res.* (1988) 8:59-81.

425. ZGOMBICK JM, SCHECHTER LE, MACCHI M, HARTIG PR, BRANCHEK TA, WEINSHANK RL: Human gene S31 encodes the pharmacologically defined serotonin 5-hydroxytryptamine $_{1E}$ receptor. *Mol. Pharmacol.* (192) 42:180-185.

426. BAGDY G, SZEMEREDI K, KANYICSKA B, MURPHY DL: Different serotonin receptors mediate blood pressure, heart rate, plasma catecholamine and prolactin responses to m-chlorophenyl-piperazine in conscious rats. *J. Pharm. Exp. Ther.* (1989) 250:72-78.

427. KLODZINSKA A, JAROS T, CHOJNACKA-WOJCIK E, MAJ J: Exploratory hypoactivity induced by m-trifluoromethylphenylpiperazine (TFMPP) and m-chlorophenylpiperazine (mCPP). *J. Neural. Trans.* (1989) 1:207- 218.

428. SAMANIN R, MENNINI T, FERRARIS A, BENDOTTI C, BORSINI F, GARATTINI S: m-Chlorophenyl-piperazine: a central serotonin agonist causing powerful anorexia in rats. *Naunyn-Schmiedebergs Arch. Pharmacol.* (1979) 308:159-163.

429. FULLER RW, SNODDY HD, MASON NR, OWEN JE: Disposition and pharmacological effects of mCPP. *Neuropharmacology* (1981) 20:155- 162.

430. KLODZINSKA A, CHOJNACKA-WOJNIK E: Anorexia induced by m- trifluoromethylphenyl-piperazine (TFMPP) in rats. *Pol. J. Pharmacol.* (1990) 42:13-17.

431. STEWART BR, JENNER P, MARSDEN CD: Induction of purposeless chewing behaviour in rats by 5-HT agonist drugs. *Eur. J. Pharmacol.* (1989) 162:101-107.

432. PIERCE PA, PEROUTKA SJ: Hallucinogenic drug interactions with neurotransmitter receptor binding sites in human cortex. *Psychopharmacology* (1989) 97:118-122.

R ferences to pat nt lit ratur :

500. SMITHKLINE BEECHAM PHARMACEUTICALS, WO 92/05170 (1991)

501. SANDOZ LTD., EP-473-550-A1 (1991)

502. ELI LILLY AND COMPANY, EP-449-561-A2 (1991).

5-HT$_{1C}$ receptors and their therapeutic relevance

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Introduction

Considerable advances have been made in the understanding of 5-hydroxytryptamine (5-HT) receptor pharmacology in the last decade. In 1979 the existence of more than one 5-HT receptor binding site was recognised for the first time when [3H]lysergic acid diethylamine (LSD) binding in the rat cortex was found to contain 5-HT and spiperone (Janssen, Figure 1) sensitive components [1]. The 5-HT sensitive component was described as 5-HT$_1$ and the spiperone sensitive portion 5-HT$_2$. Subsequently Pedigo et al. [2] showed that at least two 5-HT$_1$ receptors existed, since high affinity [3H]5-HT binding was partially displaced by spiperone. These putative receptor subtypes were termed 5-HT$_{1A}$ (spiperone sensitive) and 5-HT$_{1B}$ and can be more specifically labeled by [3H]8-hydroxy-2-di-n-propylamino-tetralin (8-OH-DPAT) [3,4] and [125I]iodocyanopindolol [5] respectively. Subsequently 5-HT$_{1C}$ [6] 5-HT$_{1D}$ [7], 5-HT$_{1E}$ [8], 5-HT$_3$ [9,10] and 5-HT$_4$ [11] receptors have been identified.

The 5-HT$_{1C}$ receptor

5-HT$_{1C}$ receptor binding studies

One area found to contain 5-HT$_1$ binding sites by autoradiographic studies was the rat choroid plexus [12]. However these '5-HT$_1$' receptors were found to bind [3H]mesulergine (Sandoz, Figure 1), a putative 5-HT$_2$ receptor ligand [13], but not the 5-HT$_2$ specific ligand [3H] ketanserin (Janssen, Figure 1) [14,15]. The 5-HT$_{1A}$ ligand 8-OH-DPAT and 5-HT$_{1B}$ ligand RU 24969 (Roussel UCLAF) also failed to displace [3H]mesulergine binding from this site which was therefore termed the 5-HT$_{1C}$ receptor [6]. The pharmacology of this receptor has a considerable similarity to that of the 5-HT$_2$ receptor. Thus most 'classical' 5-HT$_2$ receptor antagonists such as mianserin (Organon, Figure 1) and methysergide (Sandoz), are unable to discriminate between the two sites. Exceptions include ketanserin (Janssen, Figure 1), altanserin (Janssen), pirenperone (Janssen), and spiperone, all of which show selectivity for the 5-HT$_2$ receptor [16] as do two recently developed compounds RP 62203 (Rhone Poulenc, Figure 1) [17] and SR 46349B (Sanofi) [18] (Table 1). 5-HT$_2$ receptor agonists are also largely non-selective; indeed only a few compounds, whether agonist or antagonist, show selectivity for the 5-HT$_{1C}$ over the 5-HT$_2$ site (Table 1). These include 1-methyl 5-HT (one hundred-fold selective), MK 212 (Merck Sharp & Dohme, Figure 2; fifty-fold selective), (+)3-(2-aminopropyl)benz[e]indole hydrochloride (thirty-three-fold selective) [19], 1-naphthyl piperazine (1-NP) (ten-fold selective), 1-(3-chlorophenyl) piperazine (mCPP, Figure 2; ten-fold selective) and LY 53857 (Lilly; six-fold selective). 5-HT$_{1C}$ receptors have been pharmacologically characterized in pig and human choroid plexus tissue and rat cortex. There were only minor differences in the affinities of the thirteen compounds tested [20].
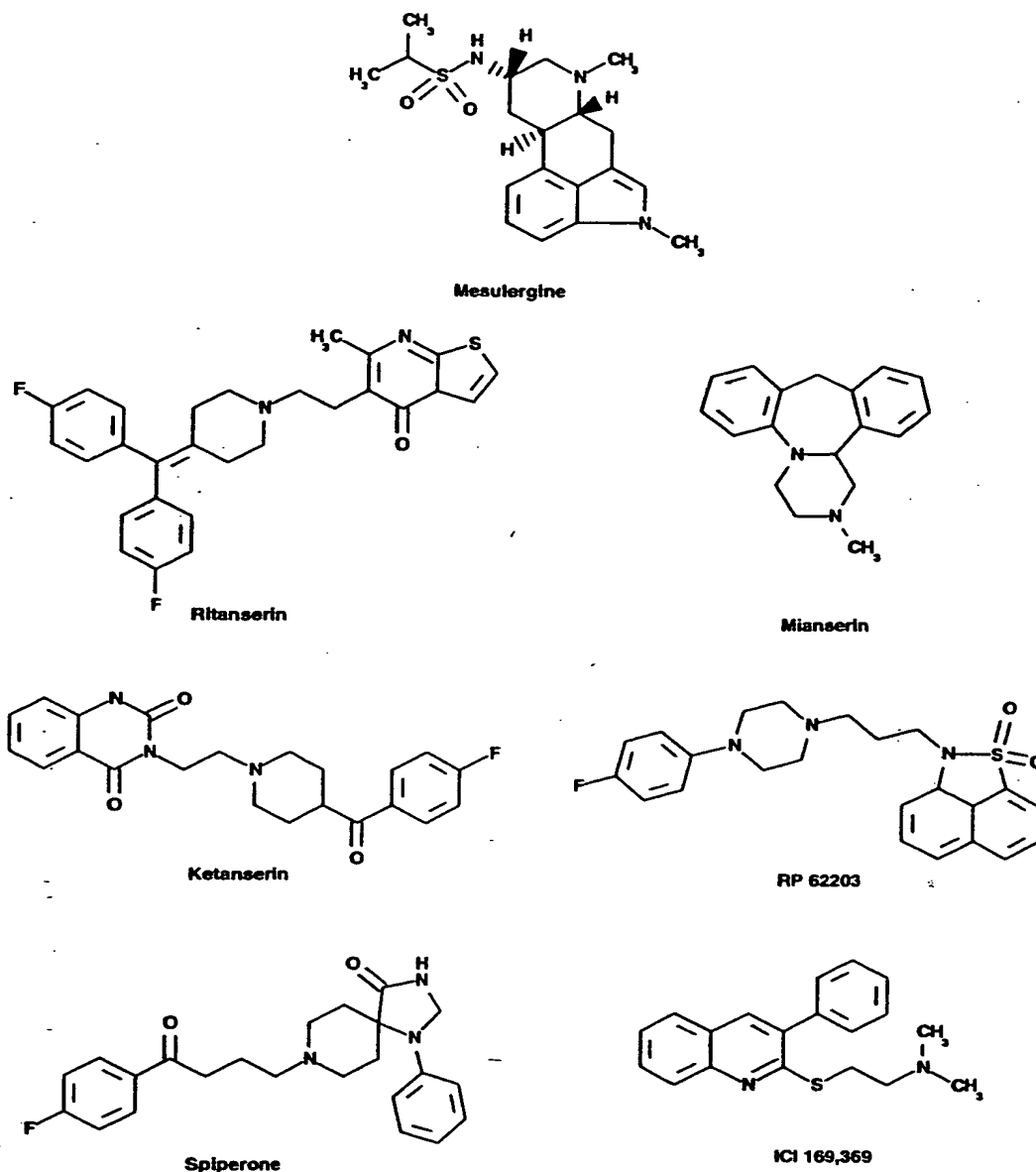
Mesulergine

Ritanserin

Mianserin

Ketanserin

RP 62203

Spiperone

ICI 169,369

Figure 1: 5-HT$_{1C}$/5-HT$_2$ receptor antagonists

Several non-selective 5-HT$_2$/5-HT$_{1C}$ receptor antagonists have been used clinically and many of the arguments advanced in the present review are based on their actions. Of these ICI 169,369 (Figure 1) and ICI 170,809 have the 'cleanest' profile. ICI 169,369 has thirteen-fold selectivity over the adrenergic α_1 receptor (Table 1). ICI 170,809 has twenty-fold higher affinity for 5-HT$_{1C}$ site over the dopamine D$_2$ site and sixty-three-fold selectivity over the adrenergic α_1 receptor and one hundred-fold higher affinity for 5- HT$_{1C}$ over the histamine H$_1$ site (Table 1). Ritanserin (Figure 1) has also been widely used clinically but has only three-fold selectivity for the 5-HT$_{1C}$ over the H$_1$ receptor and only ten-fold over the adrenergic α_1 site. It also has high affinity for dopamine D$_2$ receptors (Table 1). Lastly mianserin is equipotent at 5-HT$_{1C}$, 5-HT$_2$ and H$_1$ receptors, has six-fold selectivity over 5-HT$_3$ and sixteen-fold selectivity over adenergic α_2 sites (Table 1). Clearly none of the above drugs is an ideal tool for the study of 5-HT$_{1C}$ receptor function.

Even fewer agonists have been used, but one, mCPP, is discussed in some detail later. One problem with the interpretation of human data derived from the use of these drugs is that their affinities for human receptors may differ from their rat equivalents. One example of this is the fifty-fold higher affinity that mesulergine has for rat as opposed to human 5-HT$_2$ receptors [21]. This may give mesulergine a fifty-fold greater affinity for the 5-HT$_{1C}$ over the 5-HT$_2$ receptor in humans. In the same study ritanserin had a seven-fold lower affinity for rat than for human 5-HT$_2$ sites.

Table 1: Affinity values of 5-HT$_{1C}$ receptor antagonists for 5-HT, adrenergic α_1 and α_2, dopaminergic D$_2$ and histamine H$_1$ receptors in mammalian brain membranes.

Drug	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1C}$	5-HT$_{1D}$	5-HT$_2$	5-HT$_3$	α_1	α_2	D$_2$	H$_1$
1-NP	7.2	6.6	8.3	7.8[b]	7.2	6.9	-	-	-	-
LY 53857	6.4	5.5	8.1	-	7.3	7.5[f]	-	-	-	-
Mesulergine	6.2	4.9	8.8	5.2	8.4	-	5.3[b]	6.1[b]	6.8[b]	5.2[b]
ICI 169,369	5.3	-	8.0[c]	6.3	7.8[d]	6.0[c]	6.2[d]	5.9[d]	6.9[d]	6.0[d]
ICI 170,809	<6.0[g]	-	8.3[f]	-	9.1[g]	-	7.0[g]	-	6.1[g]	6.3[g]
Metergoline	8.1	7.4	9.2	8.3	9.0	-	7.0[a]	6.0[a]	7.2[a]	5.7[a]
Ritanserin	5.2	<4.0	8.9	5.8	8.8	5.6[g]	7.9[g]	7.1[g]	7.5[g]	8.4[g]
Methysergide	7.6	5.8	8.6	8.4	8.6	4.5	5.2[a]	5.2[a]	6.3[a]	<6.0[a]
Mianserin	6.0	5.2	8.0	6.4	8.1	7.2	6.6[a]	6.8[a]	5.8[a]	8.3[a]
SR 46349B	4.9[i]	4.8i	6.9[i]	<6.0[i]	8.2[i]	-	5.5[i]	6.0[i]	<6.0[i]	5.3[i]
RP 62203	7.1[g]	<6.0[g]	8.5[f]	-	9.9[g]	5.2[g]	8.4[g]	<6.0[g]	6.4[g]	7.3[g]
Setoperone	5.6	5.3	7.3	-	8.6	-	-	-	-	-
Pirenperone	5.9	5.3	7.3	-	8.8	-	-	-	-	-
Altanserin	5.6	6.0	6.9	-	8.6	-	-	-	-	-
Cisapride	5.7	5.2	6.3	5.3	8.1	-	-	-	-	-
Ketanserin	5.9	5.7	7.0	6.0	8.9	3.6	7.5[a]	<6.0[a]	6.3[a]	7.7[a]
Spiperone	7.2	5.3	5.9	5.3	8.8	3.6	-	-	-	-

Data taken from [16] or [423] except:

[a] Ref [15]   [b] Ref [62]   [c] Ref [100]
[d] Ref [250]   [e] Ref [103]   [f] Wood MD, personal communication
[g] Ref [17]   [h] Ref [13]   [i] pIC$_{50}$ values from [18]

The 5-HT$_{1C}$ receptor secondary messenger system

Palacios *et al.* [22] reported that activation of 5-HT$_{1C}$ in the pig choroid plexus had no effect on adenylate cyclase activity. However 5-HT was found to cause the stimulation of phospholipase C and the breakdown of phospholipids in homogenates of this tissue [23], actions usually associated with the release of Ca^{2+} ions from the intracellular stores [24,25]. This effect was potently inhibited by the non-selective 5-HT$_{1C}$/5-HT$_2$ receptor antagonist mianserin but only by high concentrations of the selective 5HT$_2$ receptor antagonist [16] ketanserin and spiperone [23], suggesting 5-HT$_{1C}$ receptor mediation. Subsequently Hoyer *et al.* [26] correlated the potency of twelve agonists and fourteen antagonists in inducing or inhibiting 5-HT-induced phosphoinositide (PI) hydrolysis in choroid plexus cells, with their

affinities for the 5-HT$_{1C}$ receptor. Since 5-HT$_2$ receptors are also coupled to a PI hydrolysis secondary messenger system this is another common feature of the two receptors.

5-HT$_{1C}$ receptor stimulation may also result in activation of Cl$^-$ channels. Application of 5-HT to Xenopus oocytes injected with rat brain or choroid plexus messenger ribonucleic acid (mRNA) causes PI hydrolysis and increased intracellular Ca^{2+} levels. This in turn was shown to cause the opening of Ca^{2+}-dependent Cl$^-$ channels [27-30]. The pharmacology of Cl$^-$ ion channel activation by 5-HT in this system is most consistent with 5-HT$_{1C}$ receptor mediation [28,29]. However there are several discrepancies such as the relatively high affinity of ketanserin and low affinity of cyproheptadine (Merck Sharp & Dohme) and mesulergine compared to that determined by receptor binding [16,28]. In Xenopus oocytes expressing mRNA from rat brain the effect of 5-HT on Cl$^-$ currents was mimicked by the intracellular application of guanosine triphosphate α (GTP)-γ-S. Both effects were blocked by injection of the Ca^{2+} chelator ethylene glycol-bis(β-aminoethyl ether) N,N,N,N-tetraacetic acid (EGTA). The effect of 5-HT was also blocked by pertussis toxin which was shown to promote the adenosine diphosphate (ADP)-ribosylation of a GI-protein [31]. This data suggests that a Ca^{2+} dependent Cl$^-$ ion channel is activated via a G-protein stimulation of phosphoinositide hydrolysis. 5-HT mediated stimulation of ion channels has also been observed in oocytes expressing mRNA from both human brain [27] and rat small intestine [32], although no pharmacological analysis was made. It remains to be seen whether 5-HT$_{1C}$ receptors in the brain are coupled to Cl$^-$ channels, or whether this coupling is artificially created by the expression of mRNA in an alien cell and its endogenous inositol phospholipid signalling system.

Evidence from Xenopus oocytes injected with both rat brain 5-HT$_{1C}$ receptor and K$^+$ channel mRNA, suggests that 5-HT$_{1C}$ receptors may modulate the function of K$^+$ channels. Thus in the presence of EGTA to suppress Cl$^-$ ion channel activation, 5-HT causes an inward current, not found in oocytes injected with either mRNA alone [33], which is due to the closing of a class of K$^+$ channels [34,35].

5-HT$_{1C}$ receptor molecular biology

The 5-HT$_{1C}$ receptor was first cloned by Lubbert *et al.* [29] from rat choroid plexus tissue. The method used involved isolating rat choroid plexus mRNAs, fractionating them by gel electrophoresis and expressing them in Xenopus oocytes where stimulation of the 5-HT$_{1C}$ receptor, formed from the desired mRNA, results in Cl$^-$ ion channel opening. The mRNA thus identified had a molecular weight of 5000 daltons. Later Julius *et al.* [36] published the amino acid sequence of this receptor which contained 460 residues. The sequence revealed seven regions of hydrophobicity each of 20-30 amino acids. These regions would be expected to associate with the hydrophobic lipid membrane to form helical transmembrane domains. This arrangement is common to all members of the G protein-coupled receptor family of membrane proteins which include the 5-HT$_2$, 5-HT$_{1A}$, adrenergic β receptor and muscarinic acetylcholine receptors amongst others. The family is so called because the response to receptor activation is indirectly mediated by a class of GTP-hydrolysing enzymes allosterically coupled to the receptor. Thus receptor stimulation activates a G protein which in turn acts upon the cellular system [37]. A more recent study has suggested that the 5-HT$_{1C}$ receptor in rat and mouse have an eighth transmembrane domain not found in other members of the G protein-coupled family [38]. Human 5-HT$_{1C}$ receptor sequences have also been recently reported [39]. Both mouse and human sequences are very similar to the rat, the mouse amino acid sequence having 97% [38] and human 90% [39] homology. These small differences have not yet been observed to have great pharmacological significance.

One observation from the sequencing of the 5-HT$_{1C}$ receptor was its resemblance to the 5-HT$_2$ receptor. In rat the overall homology is 51% as opposed to 35% for the 5-HT$_{1A}$ receptor. When the seven transmembrane domains are compared this rises to 79% homology for the 5-HT$_2$ receptor [40]. In humans total 5-HT$_2$ and 5-HT$_{1C}$ gene sequence homology was 50% and in transmembrane domains 80% [39].

It is of some interest that the 5-HT$_{1C}$ receptor gene is located on the X chromosome, unlike 5 HT$_2$ or 5-HT$_{1A}$ receptors [38]. This suggests that it may be involved in the effects of 5-HT on sexual differentiation [41].

5-HT$_{1C}$ receptor distribution

Autoradiographic studies using [^{3}H]mesulergine in rat brain have demonstrated very high densities of 5-HT$_{1C}$ receptor binding sites in the choroid plexus with roughly ten-fold lower densities in the hippocampus CA1 region, substantia nigra, globus pallidus, layer III of the cerebral cortex, olfactory cortex, lateral amygdaloid nucleus and thalamus [42]. This distribution is paralleled in mice [43]. A more detailed study of the human brain has also revealed a similar distribution. Here low levels were widely distributed in the following rank order of density: hypothalamus ventromedial nucleus > globus pallidus > hippocampus CA1 and CA3 > substantia nigra, nucleus accumbens, putamen > amygdala > thalamus. Other regions contained even lower densities [20,44].

One problem with the mapping of 5-HT$_{1C}$ receptors is the high level of non-specific binding encountered with [^{3}H]mesulergine [44]. The mapping of 5-HT$_{1C}$ mRNA is more specific and has allowed improved accuracy. Several studies have been conducted. In general these have confirmed receptor binding distributions. However some discrepancies have emerged, particularly the relatively high densities of mRNA in the septum, lateral habenula and subthalamic nucleus which are not matched by high levels of binding [43,45]. These may suggest differences in regional receptor turnover rates or reflect transport of mRNA from the cell body site of synthesis to the site of expression. Some discrepancies may be due to experimental differences. Thus Hoffman & Mezey [45] report high 5-HT$_{1C}$ mRNa levels in rat dentate gyrus not seen by Molineaux *et al.* [46] or Mengod *et al.* [43], while Molineaux *et al.* [46] report high levels in the hippocampal CA1 region which were not seen by Hoffman & Mezey [45] or Mengod *et al.* [43].

The existence of 5-HT$_{1C}$ receptors outside the brain has yet to be demonstrated. Only one model has been proposed: mediation of 5-HT-induced contractions of the rat stomach fundus [47]. This rests on the antagonist potency in this model of the older 5-HT$_{1C}$/5-HT$_2$ receptor antagonists such as mianserin, methysergide and pizotifen (Sandoz) but not specific 5-HT$_2$ receptor antagonists [48,49]. However there are a number of differences. Yohimbine and rauwolcine, which are also potent antagonists of 5-HT in the fundus [48], have little affinity for the 5-HT$_{1C}$ receptor [16]. Also many 5-HT$_{1C}$/5-HT$_2$ receptor antagonists act as non-surmountable antagonists [48] making predictions of affinity difficult. Furthermore 5-HT stimulation of the fundus appears not to cause PI hydrolysis [50]. No 5-HT$_{1C}$ mRNA was detected in the tissue [51] while extracted mRNA expressed in Xenopus oocytes inhibited cyclic adenosine monophosphate (CAMP) formation [52]. Recently Foquet *et al.* [53] reported that the rat stomach fundus gene is closely related to, but structurally distinct from, the 5-HT$_2$ and 5-HT$_{1C}$ receptor genes. This receptor was not observed in brain tissue in further studies by this group [54].
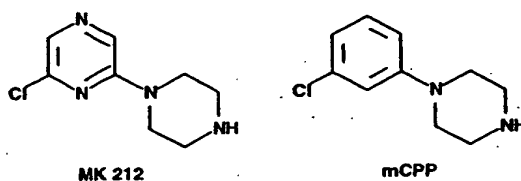
The expression of 5-HT$_{1C}$-like receptors from rat small intestine mRNA injected into oocytes [32] suggests that peripheral 5-HT$_{1C}$ receptors may exist. 5-HT$_{1C}$ receptor mediation of penile erections in rats, however, is likely to be centrally mediated [55].

MCPP - a putative 5-HT$_{1C}$ agonist

MCPP is a metabolite of the widely prescribed antidepressant trazodone (Bristol-Myers Squibb) [56]. For this reason it has been considered ethical to administer the drug to humans. MCPP has principally been considered a 5-HT$_{1B}$ agonist since it reduces 5-HT release in brain slices [57] and was observed to displace supposed 5-HT$_{1B}$ receptor binding [58], although the preparation used would have contained 5-HT$_{1C}$ receptors as well. In 1988 two prominent behavioural effects of mCPP, hypolocomotion [59] and hypophagia [60], were reported to be caused by 5-HT$_{1C}$ receptor stimulation. This was consistent with receptor binding studies in which the drug had at least ten-fold selectivity over other 5-HT receptor subtypes including 5 HT$_{1B}$ sites (Table 2). It was also consistent with the ability of mCPP to stimulate PI hydrolysis in the rat choroid plexus [61]. In this paradigm mCPP is reported to act with 65 to 90% of the efficacy of 5-HT whether rat [61] or pig [62,63] tissue is used, although both preparations have little receptor reserve [63,64]. MCPP's selectivity as a 5-HT$_{1C}$ agonist is enhanced by its actions as a silent antagonist at cortical 5-HT$_2$ receptors mediating PI hydrolysis [61], in the 5-HT$_2$-mediated head twitch model in rats [65, 66] and in the 5-HT$_2$-mediated rat jugular vein model [67]. It is also an antagonist of rat vagus nerve [10] and rat cardiac [68] 5-HT$_3$ receptors. Against bovine 5-HT$_{1D}$ receptors, Schoeffter & Hoyer [62] reported that it was a weak (30%) partial agonist with an estimated pK$_B$ of 5.1. This was somewhat less than its binding affinity for the site; pK$_I$ = 5.8–5.9 (Table 1). Recently two 5 HT$_{1D}$ receptor subtypes have been identified 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ [69]. The affinity of mCPP for cloned human 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptors is reported to be 6.6 and 6.4 respectively [69]. The slightly higher affinity of mCPP for these cloned human 5-HT$_{1D}$ receptors may reflect species differences or conceivably an artifact. MCPP has little affinity for 5-HT$_{1E}$ or 5-HT$_4$ receptors.

The ten-fold selectivity of mCPP for 5-HT$_{1C}$ over 5-HT$_{1B}$ receptors evidenced by binding studies was not observed in a comparision of its efficacy in stimulating their respective secondary messengers [62] (Table 2) although selectivity over 5-HT$_{1A}$, 5-HT$_{1D}$ and 5-HT$_2$ receptors was largely maintained. This was due to a large proportion of agonists tested having pEC$_{50}$ values in the 5-HT$_{1C}$ PI hydrolysis test roughly ten-fold lower than their binding affinities [26,62]. Since the degree of amplification needed to evoke a physiological or behavioural response in the different systems is unknown the relevance of this finding it unclear. Furthermore its relevance to mCPP's effects in man is also unclear. While 5-HT$_{1B}$ receptors are not widely distributed in human tissue [44], a species homologue, the 5-HT$_{1D\beta}$ receptor, is found [69]. At the present time no data as to the effects of mCPP on this receptor's secondary messenger systems has been reported.

MCPP has also been reported to have some affinity for the adrenergic α_2 receptor (pK$_D$ = 6.2) [70]. This is approximately forty-fold less potent than its affinity for 5-HT$_{1C}$ receptors [62], although whether mCPP acts as an agonist or antagonist at these sites is unknown. Another ambiguity is the reported release of 5-HT in vitro by mCPP [71]. The importance of this effect has yet to be clarified but implies that intact presynaptic serotonergic function would be necessary to sustain an effect of mCPP mediated in this way. MCPP has very weak affinity for the adrenergic α_1 and β receptors, and for the dopamine D$_2$, muscarinic and benzodiazepine receptors [72].

MK 212   mCPP

Figure 2: 5-HT$_{1C}$ agonists

Table 2: Profile of the *in vitro* actions of mCPP

Receptor	Affinity of mCPP		Functional model		
	Rat or Pig (pK$_I$ or pK$_D$)	Human (pIC$_{50}$)	Model	pEC$_{50}$ (pK$_B$ or pA$_2$)	Efficacy (%)
5-HT$_{1A}$	6.6[a]	6.4[b]	Adenylate cyclase	5.9	40[c]
5-HT$_{1B}$	6.5[a]		Adenylate cyclase	6.5	60[c]
5-HT$_{1C}$	7.8[a]		Phosphoinositide hydrolysis	6.9	65[c]
	7.4[d]			7.1	90[d]
5-HT$_{1D}$	5.8[a]	5.9[b]	Adenylate cyclase	5.1	30[c]
5-HT$_{1D\alpha}$	6.6[i]				
5-HT$_{1D\beta}$	6.4[i]				
5-HT$_{1E}$	5.0[j]				
5-HT$_2$	6.7[a]	6.6[b]	Phosphoinositide hydrolysis	6.1**	0[c]
5-HT$_3$	7.0[a]		Vagus nerve	6.6***	0[b]
5-HT$_4$	5.0[j]				
α_1 adrenoceptor		5.5[b]			
α_2 adrenoceptor	6.2[f]	6.2[b]			
β adrenoceptor		5.6[b]	—		
Dopamine D$_1$		5.1[b]			
Dopamine D$_2$		5.0[b]			
Benzodiazepine	< 4.0[b]				
5-HT reuptake	< 4.0[b]				
5-HT release	0.1-1mM*[g]				

* Minimum effective dose
** pK$_I$
***pA$_2$

Data taken from:

[a] [16] [b] [72] [c] [62]   [j] [AM Brown, personal communication]
[d] [63] [e] [61] [f] [70]
[g] [71] [h] [10] [i] [69]

In conclusion, mCPP is a 5-HT$_{1C}$ receptor agonist and may have some selectivity for the site. In humans this selectivity may be promoted by the apparent absence of the 5-HT$_{1B}$ receptor although this may be offset by the higher affinity of the drug for cloned human 5-HT$_{1D\alpha}$ and 5-

$HT_{1D\beta}$ receptors [44]. The effects of mCPP in man have greatly contributed to perceptions of the utility of $5\text{-}HT_{1C}$ receptor ligands.

Table 3: Behavioural effects of mCPP in rats: models of $5\text{-}HT_{1C}$ receptor function?

Paradigm	Antagonist	Dose mg/kg, *ip/sc*	Receptor Selectivity	Effect [Reference]
Hypolocomotion	Metergoline	1-5	$5\text{-}HT_1$, $5\text{-}HT_2$	Blocks[b,c] [59,229,235,426,427]
	Methysergide	5-10	$5\text{-}HT_1$, $5\text{-}HT_2$	Blocks[b,c] [427]
	Mianserin	2	$5\text{-}HT_{1C}$, $5\text{-}HT_2$, α_2	Blocks[b,c] [59,427]
	Cyproheptadine	2	$5\text{-}HT_{1C}$, $5\text{-}HT_2$, H_1	Blocks [59] / No effect[b] [427]
	Mesulergine	0.5-4	$5\text{-}HT_{1C}$, $5\text{-}HT_2$	Blocks[b] [427]
	Ketanserin	0.2-1	$5\text{-}HT_2$	No effect[c] [59,426]
	Ritanserin	0.1-2	$5\text{-}HT_2$	No effect[b] [59,426,427]
	Spiperone	0.01-0.05	$5\text{-}HT_2$, D_2	No effect?[b] [427]
	Cyanopindolol	0.2-8	$5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, β	No effect[b] [59,427]
	Pindolol	2	$5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, β	No effect[c] [59]
	Propranolol	5-16	$5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, β	No effect[c] [59] / Potentiates [235]
	ICS 205,930	1	$5\text{-}HT_3$	No effect [59,427]
	MDL 72,222	0.5	$5\text{-}HT_3$	No effect [426]
	Idazoxan	1	α_2	No effect [59,427]
	PCA	Chronic	5-HT lesion	Blocks [427]
	PCPA	Chronic	5-HT depletion	No effect [Unpublished observation]
Hypophagia	Metergoline	1-5	$5\text{-}HT_1$, $5\text{-}HT_2$	Blocks [d] [60,428,429]
	Mianserin	2-5	$5\text{-}HT_{1C}$, $5\text{-}HT_2$ α_2	Blocks [d] [60]
	Cyproheptadine	10	$5\text{-}HT_{1C}$, $5\text{-}HT_2$ H_1	No effect [60]
	Mesulergine	0.2	$5\text{-}HT_{1C}$, $5\text{-}HT_2$	Blocks [d] [60]
	Ketanserin	0.2	$5\text{-}HT_2$	No effect [e] [60]
	Ritanserin	0.6	$5\text{-}HT_2$	No effect [e] [60]
	Cyanopindolol	8	$5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$ β	Blocks [e] [60]
	Propanolol	16	$5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$ β	Blocks [60]
	ICS 205,930	1	$5\text{-}HT_3$	No effect [60]
	Idazoxan	1	α_2	No effect [60]
	Median Raphe lesion		Lesion	No effect [428]

Table 3: (cont.)

Paradigm	Antagonist	Dose mg/kg, ip/sc	Receptor Selectivity	Effect [Reference]
Penile Erection	Metergoline	0.02-0.2	5-HT$_1$, 5-HT$_2$	Blocks [231]
	Mianserin	0.02-0.2	5-HT$_{1C}$, 5-HT$_2$ α_2	Blocks [231]
	Cyproheptadine	0.1-1.0	5-HT$_{1C}$, 5-HT$_2$ H$_1$	Blocks [231]
	Mesulergine	0.02-0.2	5-HT$_{1C}$, 5-HT$_2$	Blocks [231]
	Ketanserin	0.5-1.0	5-HT$_2$	No effect [231]
	Ritanserin	0.1-0.5	5-HT$_2$ [a]	Blocks [231]
	Spiperone	0.1-1.0	5-HT$_2$, D$_2$	No effect [231]
	GR 38032F	1-10	5-HT$_3$	No effect [231]
Hyperthermia	Metergoline	0.5	5-HT$_1$, 5-HT$_2$	Blocks [233]
	Ritanserin	0.6[a]	5-HT$_2$	No effect [233]
	Pindolol	4	5-HT$_{1A}$, 5-HT$_{1B}$ β	No effect [233]
	Propanolol	6	5-HT$_{1A}$, 5-HT$_{1B}$ β	No effect [233]
Purposeless Chewing	Mianserin	1	5-HT$_{1C}$, 5-HT$_2$	Blocks [431]
	Ketanserin	5	5-HT$_2$	No effect [431]
	Spiperone	0.5	5-HT$_2$, D$_2$	No effect [431]
	ICS 205,930	10	5-HT$_3$	No effect [431]
	(−)Propranolol	20	5-HT$_{1A}$, 5-HT$_{1B}$ β [f]	Blocks [431]

[a] Since the *in vivo* ID$_{50}$ value for ritanserin against mCPP-induced hypophagia was 4.6 mg/kg *sc* [66], doses below this may be 5-HT$_2$ selective.

[b/c] Similar results obtained against TFMPP-induced hypolocomotion. Results from [b] [427] and [c] [229].

[d] Similar results obtained against TFMPP-induced hypophagia in freely feeding rats [430].

[e] Ketanserin 2.5 mg/kg partially blocked, cyanopindolol had no effect and ritanserin 0.5 and 1 mg/kg *ip* had an inverse dose related effect on TFMPP-induced hypopgagia [430].

[f] As (−)propranolol does not have pronounced specificity for 5-HT$_{1A}$ and 5-HT$_{1B}$ over 5-HT$_{1C}$ sites [16], this dose may have blocked them all.

Possible therapeutic targets of 5-HT$_{1C}$ receptor ligands:

Anxiety

Anxiety is widely observed in nearly all forms of mental illness. It is present in its purest form in anxiety disorders but is a noted feature of depression, schizophrenia and personality disorders. Four major types of anxiety have been characterised; generalised anxiety disorder (GAD), panic disorder with or without agorophobia, obsessive compulsive disorder (OCD), and other phobias. Several problems are associated with existing therapy. One of the most serious is the development of dependence in patients on long term benzodiazepine treatment. This leads to the induction of a marked anxiety on withdrawal [73]. Other problems include sedation and the interaction of this class of drugs with alcohol and barbiturates. Furthermore benzodiazepines are ineffective in the treatment of OCD [74], which only responds to chronic treatment with some antidepressants [75] and is then only partly effective. Chronic

antidepressant treatment is also efficacious in panic disorder [76-78]. However the side effect profile of this class of drugs (which includes anticholinergic, sedative and postural hypotensive effects for tricyclic antidepressants and hypotension and insomnia for monoamine oxidase inhibitors (MAOI)) has prevented their widespread use in these indications. Even the selective 5-HT reuptake inhibitor (SSRI) fluoxetine (Lilly) is associated with insomnia, nausea and asthenia [79].

Generalised anxiety disorder

Administration of mCPP to human volunteers caused anxiety [80-84]. In some subjects panic attacks were experienced [84,85]. The anxiogenic response to mCPP is accompanied by an increase of the stress sensitive hormones adrenocorticotrophic hormone (ACTH), cortisol and prolactin [80,86,87]. However there is some uncertainity over whether the hormonal changes are secondary to anxiety or not. Two studies of prolactin release suggest that it does follow peak anxiety [81,86] while one does not [84], although significant anxiety was not seen in this study.

MCPP administration to rats also induces anxiogenic-like responses in both the social interaction (SI) [88,89] and the elevated X-maze [Kennett, unpublished observations] models of anxiety, and decreases punished responding in a pigeon conflict model [90]. However in both the rat Geller-Seifter [91] and acoustic startle [92] models of anxiety the actions of mCPP were obscured by sedative or motor effects.

The anxiogenic response to systemic mCPP in the SI test was replicated after intra-hippocampal, but not intra-amygdaloidal, infusion [89]. This region has long been associated with the control of anxiety and is known to contain 5-HT$_{1C}$ receptors [42,43,45,46]. The effect of mCPP, at least in the elevated X-maze, is not secondary to the release of 5-HT as it is not opposed by pretreatment with the 5-HT synthesis inhibitor p-chlorophenylalanine [Kennett, unpublished observations].

The pharmacology of the anxiogenic responses to mCPP in the rat SI and elevated X-maze tests is consistent with 5-HT$_{1C}$ mediation. Thus in the SI test it is blocked by the non specific 5-HT$_2$/5-HT$_{1C}$ receptor antagonists mianserin, cyproheptadine and metergoline (Farmitalia) (Table 1) but not by the selective 5-HT$_2$ antagonist ketanserin (Table 1) or by the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor antagonists [16] cyanopindolol (Sandoz) and (-)propranolol (ICI) [88]. The action of mCPP in the X-maze was similarly opposed by the non-selective 5-HT$_2$/5-HT$_{1C}$ receptor blockers mianserin, LY 53857 and 1-NP [16], but not by the selective 5-HT$_2$ antagonists ketanserin and altanserin [16] nor by the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor blockers pindolol (Sandoz) [16] and cyanopindolol [Kennett, unpublished observations]. The effects of mCPP in both models was opposed by the benzodiazepine anxiolytic chlordiazepoxide (Roche) [88,93] reinforcing the interpretation that mCPP is anxiogenic. The anxiogenic effects of mCPP in both models were also attenuated by the 5-HT$_3$ receptor antagonists [16,94] ICS 205,930 (Sandoz) [88] and BRL 46470A (SmithKline Beecham) [93] in the SI and X-maze tests respectively. This is likely to be caused by the anxiolytic profile of these drugs [93,95]. Indeed mCPP might have more pronounced anxiogenic activity if it had less affinity for the 5 HT$_3$ site at which it is an antagonist (Table 1).

The results from rat models are consistent with the available clinical data. Thus the anxiogenic responses to mCPP have been reported to be blocked by the non-selective 5-HT$_1$ and 5-HT$_2$ receptor antagonists metergoline [85,96] and methysergide [85] and by the 5-HT$_2$/5-HT$_{1C}$ receptor antagonist ritanserin (Janssen) [83]. This last report is of considerable interest, as

ritanserin has little affinity for other 5-HT receptor subtypes [16] and mCPP itself is a 5-HT$_2$ antagonist (see section on mCPP as a putative 5-HT$_{1C}$ agonist).

The effects of antagonists on neuroendocrine responses to mCPP are similar. Metergoline and ritanserin both attenuate mCPP-induced prolactin secretion [83,87,96,97]. They also blocked the increase in cortisol [83,87,97]. Metergoline blocks the ACTH response as well [87]. Methysergide, however, was reported to block prolactin but not cortisol responses to mCPP [97].

Mediation of the anxiogenic effects of mCPP by 5-HT$_{1C}$ receptor activation suggests that their blockade would be anxiolytic provided that some tone is exerted through the receptors under normal and/or anxiety provoking conditions. This hypothesis is supported by evidence from animal studies. In two recent studies [98,99], five non-selective 5-HT$_2$/5-HT$_{1C}$ receptor antagonists, mianserin, 1-NP, ICI 169,369 (ICI), LY 53857 and pizotifen, (Table 1, [16,100]), were found to have anxiolytic-like actions in both the SI and Geller Seifter conflict tests. Compounds that did not share this property include: the selective 5-HT$_2$ antagonists ketanserin and altanserin, (Table 1); 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor antagonists pindolol and cyanopindolol [16]; adrenergic α_2 receptor antagonist idazoxan (Reckitt and Colman) [101] or adrenergic α_2 antagonist and 5-HT$_{1D}$ partial agonist yohimbine [101,102]; and H$_1$ antagonist mepyramine (May and Baker). The possibility of 5-HT$_3$ mediation of the effects is also unlikely as ICI 169, 369 [103] and LY 53857 (Table 1) have low affinity for this site, and 5-HT$_3$ antagonists are inneffective in the Geller-Seifter test [104,105]. Since the two tests have different motivational and aversive components the conclusion that these non-selective 5-HT$_{1C}$ receptor antagonists are anxiolytic is strengthened. Similar findings have not been universally reported. The 5-HT$_2$/5-HT$_{1C}$ receptor antagonist ritanserin, for instance, was inactive in one SI test [106], although the conditions used were inappropriate for the detection of anxiolysis [98]. The compound was active in one rat conflict procedure [107] but not in three others [108,109], although the paradigms used in the latter study were insensitive to benzodiazepines also. However, in the pigeon conflict test, claimed to be more sensitive to serotonergic drugs, ritanserin has shown an anxiolytic profile [90,109]. Mianserin, too, had no effect on SI where relatively high doses were used [110] but was active in the Geller-Seifter test when lower doses, similar to those of Kennett [98] or Kennett et al. [99], were used [111]. Another 5-HT$_2$/5-HT$_{1C}$ receptor antagonist cyproheptadine [16] was also effective in some [112,113] but not all [108] conflict tests, while ICI 169,369 had some activity in the pigeon conflict test [114]. The non-specific 5-HT$_1$ and 5-HT$_2$ antagonists methysergide and metergoline [16] were not active in the SI test, albeit under different conditions [115], but were active in conflict tests [116-120]. The selective 5-HT$_2$ receptor antagonist ketanserin has also shown an anxiolytic profile in the pigeon conflict model [90]. This may reflect species differences in the 5-HT$_{1C}$ receptor, or in the metabolism and disposition of ketanserin.

Another rat model claimed to be relevant to anxiety is the response to electrical stimulation of the periaqueductal gray (PAG). In humans this elicits unpleasant and fearful sensations [121] and in animals causes vigorous flight or defense reactions [122]. In this model mCPP acts as an anti-aversive agent; 5-HT$_2$/5-HT$_{1C}$ antagonists mianserin, cyproheptadine and ritanserin as pro-aversive agents; and selective 5-HT$_2$ antagonists ketanserin, pirenperone and spiperone as anti-aversive agents [123]. Since mCPP is clearly anxiogenic both clinically and in other animal models the relevance of this paradigm is uncertain, but it may apply to a particular type of anxiety. Recently Beckett et al. [124] have reported mCPP to be pro-aversive when the PAG was chemically stimulated by homocysteic acid. This effect was blocked by mianserin.

The difference between these results and those obtained using electrical stimulation of the PAG may be due to the stimulation of fibres of passage by the latter technique.

Taken as a whole these results suggest that 5-HT$_{1C}$ antagonists are anxiolytic in at least some animal models. This is consistent with reports of the clinical anxiolytic properties of mianserin [125–128] and the effectiveness of ritanserin in generalised anxiety disorder [129–131]. Metergoline, however, is not anxiolytic [75] and may be anxiogenic clinically [132]. This may reflect its non-specificity for 5-HT$_1$ subtypes [16] and possibly the different distribution of receptors in man and rat. It is of considerable interest that selective 5-HT$_{1C}$ receptor antagonists have been claimed to possess anxiolytic activity, being active in the SI and Geller-Seifter test, in a recent SmithKline Beecham patent [500].

Panic Disorder

The administration of mCPP to normal volunteers evoked anxiety resembling panic attacks in some subjects [84,85]. In panic disorder patients, mCPP was found to induce panic attacks in roughly half of those treated. These were reportedly indistinguishable from those normally experienced [81,85,133–135]. The increase in anxiety and panic reported by these patients was also greater than that of healthy volunteers [85,133,134] although this did not reach significance in the study by Charney et al. [81]. However this group may have achieved a supramaximal response.

Neuroendocrine responses to mCPP in panic disorder patients followed a similar pattern. Thus Kahn et al. found that plasma cortisol responses to mCPP were enhanced [133], as were ACTH and prolactin in female, but not male panic disorder patients [136]. However cortisol, prolactin and growth hormone responses were not different from healthy volunteers in the study of Charney et al. [81] as observed for the anxiety response.

The above evidence has been used to argue the existence of hypersensitive 5-HT receptors in panic disorder. Since the anxiogenic effects of mCPP are probably 5-HT$_{1C}$ receptor mediated (see above) these may be the hypersensitive 5-HT receptors in panic disorder. However the enhanced responses to mCPP could instead be secondary to hypersensitive anxiety mechanisms distal to 5-HT$_{1C}$ receptors themselves. This view is supported by the ability of caffeine [135,137,138], yohimbine [139] and lactate [140], anxiogenic agents with differing modes of action to mCPP, to also induce a greater degree of anxiety in panic disorder patients, although not all induce robust increases in cortisol or prolactin [135]. The hypothesis may be further supported by the lack of clinical efficacy of the 5-HT$_{1C}$ and 5-HT$_2$ receptor antagonist ritanserin in panic disorder [141] although an earlier open trial of the drug did suggest some benefit [142]. Furthermore the efficacy of tricyclic antidepressants [76] and the specific 5-HT reuptake inhibitor fluoxetine [77,78] after chronic administration may be mediated by down regulation of 5-HT$_{1C}$ receptors (see section on depression).

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is characterised by obsessions (recurrent, intrusive thoughts) and compulsions (repetitive behaviours) such as ritualistic washing or checking which the patient recognises as senseless. The patients experience significant anxiety but the most common complication of primary OCD is depression [75]. OCD is refractory to benzodiazepine anxiolytics, despite reduced anxiety levels [74]. However chronic treatment with the antidepressant chlorimipramine (Geigy) [143,144] was found to ameliorate symptoms to a greater degree than other tricyclic and MAOI antidepressants [145]. Since chlorimipramine is a relatively selective 5-HT reuptake inhibitor [146] this suggested that a defective 5-HT

system might be involved, as did the effectiveness of treatment with the 5-HT precursor tryptophan [147] and the correlation of clinical efficacy of chlorimipramine with reduced CSF 5-hydroxyindoleacetic acid levels, but not plasma levels, of the drug [148]. Subsequently, chronic treatment with specific 5-HT reuptake inhibitors such as fluoxetine, zimeldine (Astra), sertraline (Pfizer) and fluvoxamine (Duphar) were also found to be effective anti-obsessional treatments [149,150] while the 5-HT releaser fenfluramine (Servier) can augment the therapeutic action of chlorimipramine [151]. Unfortunately, none of the treatments are effective in more than 50% of the patients and this is only reached after approximately 6 weeks treatment [145,149]. MAOIs, which acutely enhance extraneuronal 5-HT, are also clinically effective in OCD [145] although not in all studies [143]. But noradrenergic reuptake inhibitors are not effective[145].

The administration of mCPP orally to OCD patients provoked anxiety and this response was greater than in healthy volunteers [152]. The drug also exacerbated obsessive compulsive symptoms [96,152–154] which in some cases had been absent for several months, although this did not occur in the study of Charney et al. [155] in which intravenous administration was used. None of the studies reported the induction of panic attacks in OCD patients. The effect of mCPP on OCD symptoms was antagonised by metergoline [75,96] which is a non-specific 5-HT$_1$/5-HT$_2$ receptor antagonist [16]. Since mCPP and metergoline act as agonist and antagonist respectively at 5-HT$_{1C}$ receptors, these findings may suggest that the receptors are in some way hypersensitive in OCD patients. Chronic administration of specific 5-HT reuptake inhibitors such as fluoxetine or MAOIs might therefore act by down-regulating these receptors, as suggested by evidence outlined in the section on depression and by the ability of chronic administration of fluoxetine and chlorimipramine to desensitise the behavioural effects of mCPP in OCD patients [157,158]. However not all evidence supports this hypothesis. Obsessive compulsive symptomology was not induced by MK 212 [156], an agonist at 5-HT$_{1C}$ receptors [61] with roughly fifty-fold selectivity over 5-HT$_2$ receptors [16]. This may reflect the drug's poor selectivity over 5-HT$_{1A}$ receptors [16] or its even higher affinity for the 5-HT$_3$ receptor (Table 3, [159]). Its affinity for many other sites is unknown and could also influence its effects on OCD patients, although in rats the stimulus cue of MK 212 generalized to mCPP and was blocked by metergoline and methysergide but not by specific 5-HT$_2$ receptor antagonists [160]. Another difficulty for the 5-HT$_{1C}$ hypothesis of OCD is the failure of acute fenfluramine, the 5-HT releaser, to induce OCD symptomology in OCD patients [154,161]. Although this type of drug might be expected to stimulate many 5-HT receptor subtypes simultaneously, which could account for this finding, it too produces a stimulus in rats which generalizes to mCPP [160] and induces anxiety in rats by 5-HT$_{1C}$ receptor stimulation [162]. It also has reasonable affinity for the 5-HT$_{1C}$ receptor itself [163].

Evidence from neuroendocrine responses to mCPP is also inconsistent with 5-HT$_{1C}$ receptor hypersensitivity in OCD. Patients had reduced cortisol responses to mCPP [152,156] and reduced prolactin responses in some [154,155,158] but not in all [152,154] studies. Responses of both hormones to MK 212 were also blunted [156]. Furthermore, although chronic fluoxetine [157] and chlorimipramine [158] abolished the ability of mCPP to increase obsessive and compulsive symptoms and anxiety, cortisol and prolactin responses were potentiated in the fluoxetine study [156], although increased plasma levels of mCPP could have been responsible [153]. Neuroendocrine evidence, therefore, suggests that 5-HT$_{1C}$ receptors may be subsensitive in OCD in direct contrast to the behavioural data.

These apparent contradictions may be explained if the involvement of 5-HT$_{1C}$ receptors in OCD symptomology resides in specific brain regions or if the hormonal responses to mCPP are not 5-HT$_{1C}$ receptor mediated. The latter possibility seems unlikely, as clinically mCPP-

induced cortisol and prolactin secretion are blocked by metergoline [87,97] and the relatively selective $5-HT_2/5-HT_{1C}$ receptor antagonist ritanserin [83], although methysergide only blocked the prolactin response [97]. A third possibility is that a functional supersensitivity, which is either proximal or distal to the $5-HT_{1C}$ receptors, underlies OCD and that the receptors themselves are down regulated by compensatory mechanisms.

Table 4: Pharmacology of trifluoromethylphenylpiperazine (TFMPP), MK 212, Quipazine, 2,5-dimethoxy-4-iodoamphetamine (DOI) and (–)2,5-demethoxy-4-iodoamphetamine (–)(DOM); agonists at $5-HT_{1C}$ receptors

Receptor		$5-HT_{1A}$	$5-HT_{1B}$	$5-HT_{1C}$	$5-HT_{1D}$	$5-HT_{1D\alpha}$	$5-HT_{1D\beta}$	$5-HT_{1E}$	$5-HT_2$	$5-HT_3$
Drug	Parameter									
TFMPP	pK_D	6.5	6.9	7.3	6.6	7.1[g]	6.9[g]	5.2[b]	6.6[a] 6.1[b] Ant[b]	
	pEC_{50}	6.7	6.9	6.8	5.8					
	Efficacy	67.1	74.3	59.2	54.2					
MK212	pK_D	5.3[c]	5.0[c]	6.2[c]	>5.0[f]			>50[k]	4.8[c] 4.7[b] 80[b]	7.5[i]
	pDC_{50}			6.1[b]						
	Efficacy			90[b]						
Quipazine	pK_D	5.5	6.5	6.7	5.9				6.2	8.5
	pEC_{50}	5.2	6.2	6.2	5.7				5.0	
	Efficacy	Ant	Ant	63	Ant				80	Ant
DOI	pK_D	4.7[j]		7.8[d]	5.6[j]			5.5[b]	7.5[j]	
	pEC_{50}			7.0[d]						
	Efficacy			58[d]						
(–)DOM	pK_D			6.8[e]						
	pEC_{50}			6.1[e]						
	Efficacy			85[e]						

Values for pEC_{50} and efficacy (E_{max} as a percentage of that for 5-HT) for agonist activity, pK_B for antagonist efficacy and pK_D from receptor binding studies are given. The functional assay for $5-HT_{1A}$, $5-HT_{1B}$ and $5-HT_{1D}$ receptor was inhibition of forskolin-stimulated adenylate cyclase activity. The assay for $5-HT_{1C}$ and $5-HT_2$ receptor function was stimulation of basal inositol phosphate accumulation in choroid plexus and cortical tissue, respectively. All data taken from [62] except:

[a] [16]   [b] [61]   [c] [424]
[d] [26]   [e] [64]   [f] G Price; personal communication
[g] [69]   [h] [425]   [i] [159] (pIC$_{50}$)   [j] [432]   [k] [AM Brown, Personal communication]

The effect of mCPP on OCD symptoms, unlike its actions in panic disorder (see above), is not typical of other anxiogenic drugs. Thus yohimbine [164], lactate [165] and caffeine [166] cannot induce or exacerbate obsessive compulsive symptomatology, suggesting the existence of a specific dysfunction. Interestingly, these symptoms are not induced in healthy volunteers. While the evidence points to this dysfunction possibly involving $5-HT_{1C}$ receptors, there is less evidence that an antagonist of these receptors would be of therapeutic benefit. Metergoline, the only $5-HT_{1C}$ receptor antagonist studied to date, was found to modestly reduce obsessive compulsive symptoms in one study [75] but not in a second [96]. The lack of effect of metergoline could reflect the drug's lack of spef-icity for $5-HT_{1C}$ receptors [16] (Table 1); indeed, in some clinical studies it was itself anxiogenic [132] and in one study it reversed the therapeutic action of chlorimpiramine, increasing anxiety and OCD symptomatology [167]. One possible property of metergoline that would be more prevalent in humans than in rodents is its agonist activity at $5-HT_{1D}$ receptors [168], the effects of which are, as yet, unknown. If $5-HT_{1D}$ receptor stimulation can induce OCD symptomatology, as has been suggested by Zohar & Kindler [169], this might underlie the action of mCPP which has agonist properties at $5-HT_{1D}$ receptors and relatively high affinity for the $5-HT_{1D\alpha}$ and $5-HT_{1D\beta}$ cloned human

receptors (Table 2). It might also be consistent with the failure of MK 212 to precipitate OCD symptomatology [156] as this drug has low affinity for the 5-HT$_{1D}$ receptor (Table 3), although its affinity for human 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptors is unknown. However the effects of metergoline on OCD symptomatology are inconsistent (as outlined above) and yohimbine, another 5-HT$_{1D}$ partial agonist [168], had no effect [164].

Another possibility is that metergoline could be a 5-HT$_{1C}$ agonist at the human receptor. Alternatively the effects of 5-HT reuptake inhibitors and MAOIs could be caused by effects on sites other than the 5-HT$_{1C}$ receptor.

Drugs of abuse

Alcoholism

Alcoholism is estimated to have a lifetime occurrence of 11-16% of the American population [170], and 5-HT has long been thought to influence this condition. Low cerebral spinal fluid (CSF) levels of the principal metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), have been observed in alcoholics [171,172]. This would seem to be trait-dependent as they were also observed in abstinent alcoholics [171] or in those suffering from withdrawal symptoms after one week of abstinence [173]. Banki [174,175] reported a negative correlation between 5-HIAA levels and number of days of abstinence.

Animal studies have provided further evidence. Levels of 5-HT and 5-HIAA were found to be reduced in some brain regions of alcohol-preferring rats [176]. Acutely, alcohol increases 5-HT release [177] and metabolism [178,179] in the striatum and increases 5-HIAA levels in several other brain regions including the nucleus accumbens [176] while reduced 5-HT turnover has been observed after chronic treatment [180]. Low 5-HT function has therefore been proposed to promote alcohol consumption. Treatments which increase serotonergic function might thus be expected to reduce alcohol consumption, and this has indeed been reported. Administration of the 5-HT precursors tryptophan [181] or 5-hydroxytryptophan (5-HTP) [176], the 5-HT releasing agent fenfluramine [176] and the 5-HT reuptake inhibitors fluoxetine [182–184] and sertraline [185], all reduce alcohol consumption when given acutely to rats. Intra-nucleus accumbens 5-HT has a similar effect [186]. The 5-HT$_{1A}$ agonist 8-OH-DPAT [176,187,188], 5-HT$_2$ and 5-HT$_{1C}$ agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) (Table 3, [176]) and 5-HT$_{1B}$ and 5-HT$_{1C}$ agonist 1-(3-(trifluoromethyl)phenyl)piperazine (TFMPP) (Table 3, [176]) also reduce consumption. Conversely, treatments that reduce 5-HT function, such as the 5-HT depletor para-chlorophenylalanine (PCPA) [189,190], enhance consumption. However the non-specific 5-HT$_1$ and 5-HT$_2$ receptor antagonists methysergide and metergoline [191,192] had no effect, while the 5-HT neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) had inconsistent effects [193,194].

Clinical trials are in agreement with results from animal models. In particular the 5-HT reuptake inhibitors fluoxetine, zimelidine, and citalopram (Lundbeck) all reduced the mean daily alcohol consumption of moderate alcoholics. The magnitude of this effect while consistently observed was only 9-17% [195–197]. Interestingly, the effect had a rapid onset, unlike the antidepressant actions of these drugs. This suggests mediation by increased synaptic cleft 5-HT levels. The 5-HT$_{1A}$ receptor agonist buspirone (Bristol-Myers Squibb) has also been shown to have modest clinical efficacy [198–200]. This could be mediated either by stimulation of postsynaptic 5-HT$_{1A}$ receptors, by desensitisation of cell body autoreceptors and hence enhanced 5-HT release [201], or acutely by stimulating these autoreceptors and hence decreasing 5-HT release.

In view of the above evidence that enhanced 5-HT suppresses ethanol intake, the effects of mCPP on alcoholics are surprising. The drug was reported to induce an alcohol-like 'high' feeling in alcohol abstaining alcoholics and, in a third of the subjects, induced a craving to drink alcohol [202]. One explanation for these results, proposed by Sellers et al. [203], is that mCPP can induce an ethanol-like stimulus. This is supported by the reported similarity between the ethanol cue in a rat drug discrimination paradigm and that of TFMPP [204], a 5-HT$_{1C}$/5-HT$_{1B}$ agonist resembling mCPP both pharmacologically (Table 3) and behaviourally in rats [59,60,88,205]. The perception of an alcohol-like stimulus in the absence of the full pharmacological effect may therefore cause craving.

An alternative explanation is that alcoholism is related to obsessive compulsive disorder [206]. Like alcoholism, OCD can be characterised by low 5-HT function [144,147], is ameliorated by specific 5-HT reuptake inhibitors (albeit after chronic administration [149]) and can be precipitated by mCPP (see above). It has also been suggested that the craving response to mCPP is secondary to the induction of anxiety [203], since alcoholism often coexists with anxiety [207]. This seems the least likely explanation, as anxiety induction was not noted in the Benkelfat et al. [202] study. However, the clinical efficacy of buspirone might be secondary to anxiolysis [208].

The pharmacology of mCPP (Table 2) suggests that 5-HT$_{1C}$ receptors may account for these actions. Recent reports that the 5-HT$_{1C}$ and 5-HT$_2$ antagonist (Table 1) ritanserin can reduce alcohol preference in rats [209] are possibly consistent with this. The effect was accompanied by increased water intake. It was not mediated by alcohol aversion nor by altered alcohol metabolism, and was not associated with body weight changes [209]. It may therefore specifically affect addictive mechanisms. Although this study reported effects at low doses, which might not be expected to block 5-HT$_{1C}$ receptors in vivo [66], only high 5-HT$_{1C}$ receptor blocking doses [66] were effective in a second model [210]. Ritanserin was also found to markedly reduce the alcohol intake of a small group of chronic alcoholics [211]. These patients reported that they had little difficulty in containing their consumption even after two weeks withdrawal from the drug. Mediation of these effects by 5-HT$_2$ receptor blockade seems unlikely: firstly mCPP is a 5-HT$_2$ receptor antagonist (Table 2), and secondly the specific 5-HT$_2$ receptor antagonist ketanserin (0.4 mg/kg po one hour pretest) did not affect rat alcohol preference in a recent study [210]. The reported ability of DOI and TFMPP, agonists at 5-HT$_{1C}$ receptors, to reduce alcohol consumption in rat models [176] may be due to their anorexic [205,212], sedative [59,213] or, in the case of DOI, hallucinogenic [214] actions. These effects were not reported in the clinical study of Benkelfat et al. [202]. The predominance of the craving response to mCPP in alcoholics may suggest hypersensitive 'craving' mechanisms.

In conclusion, the opposing effects of mCPP and ritanserin, both clinically and in animal models, must be considered evidence of possible 5-HT$_{1C}$ involvement. Further evidence must await the development and testing of more selective compounds. Indeed the effects of mCPP and ritanserin, while seemingly behaviourally specific and opposite, may be unrelated, as may be the case if ritanserin were acting as an anxiolytic (see above). The opposite nature of the effects of treatment which enhance 5-HT function such as 5-HT reuptake mechanisms (see above) and the mCPP/ritanserin studies, suggest the existence of several serotonergic mechanisms modulating alcoholism. When 5-HT function is enhanced at several receptor subtypes simultaneously the net result is alcohol intake inhibition. Conceivably this also occurs when 5-HT$_{1C}$ receptors are selectively blocked. Given the modest clinical efficacy of 5-HT reuptake inhibitors there is considerable scope for new forms of treatment.

Other drugs of abuse

In addition to its effects on alcohol abuse, ritanserin has been anecdotally noted to be of use in patients withdrawing from other drugs of abuse [214]. This has led to an examination of its actions in rat models of cocaine and opiate dependence. Ritanserin was found to reduce both cocaine and fentanyl (Janssen) preference of rats [216,217]. The magnitude of the effect on cocaine was less than that observed for alcohol but greater than that observed with fentanyl [217]. This probably reflects the degree of reinforcement engendered by the drugs. Ritanserin does not interact with the cues for cocaine or fentanyl [216,217] which argues against any direct effects of the drug. Since drugs of abuse are thought to induce reinforcing effects by activating the dopamine reward pathways of the nucleus accumbens [218], it is of interest that ritanserin does not affect intracranial self-stimulation [216,217] which is thought to act on the same system. Ritanserin may therefore have a specific action on a reinforcing pathway common to drugs of abuse and perhaps distal to dopaminergic mechanisms of the nucleus accumbens. Whether this is 5-HT$_{1C}$ or 5-HT$_2$ receptor mediated is not yet clear.

Depression

A large body of evidence suggests that the serotonergic system is defective in depression. Most neurochemical and neuroendocrine studies of depressive patients are consistent with the existence of a serotonergic deficit, while SSRIs and MAOIs are clinically effective antidepressants and both increase extraneuronal 5-HT acutely (for review, see [219]).

One argument in favour of 5-HT$_{1C}$ receptor involvement in depression is the clinical efficacy of three 5-HT$_2$/5-HT$_{1C}$ receptor antagonists: mianserin [125,126,128], cyproheptadine [220] and ritanserin [221-223]. However, none of these drugs has been reported to exert immediate therapeutic action [221,223]. This may argue against simple 5-HT$_{1C}$ receptor blockade as a mode of action. Alternatively it might reflect a property of the disease state.

Clinically, the effect of treatments expected to enhance 5-HT$_{1C}$ function is also unclear. Thus mCPP administration to healthy volunteers did not cause depressive symptoms in most studies [80,81,84,134,224-226], with one exception [86]. In addition it does not potentiate depression in depressive patients and neither cortisol nor prolactin responses in these patients differed from that of healthy volunteers [133,134,226]. Indeed when given subchronically it ameliorated depressive symptomatology in elderly depressives [227]. These findings argue against direct 5-HT$_{1C}$ involvement in depression. However antidepressants may exert their therapeutic efficacy after chronic administration through adaptive changes to the serotonergic system [228], and, in particular, to the 5-HT$_{1C}$ receptor, as suggested by studies in rats. These involve models of 5-HT$_{1C}$ receptor function and are summarised in Table 5. Chronic treatments with the MAOIs phenelzine (Parke-Davis) or nialamide (Pfizer) have been reported to desensitise mCPP-induced hypolocomotion [229], a putative 5-HT$_{1C}$ mediated behaviour (Table 3, [59]). The MAOI tranylcypromine (SmithKline Beecham) reduced mCPP-induced penile erections [230], another putative 5-HT$_{1C}$ mediated response (Table 3, [231]) after chronic treatment, while chronic clorgyline reduced mCPP-induced hypophagia [232] and hyperthermia [233]. Of these last two paradigms mCPP-induced hypophagia is relatively well characterised as 5-HT$_{1C}$ mediated (Table 3, [59,66]) while hyperthermia is likely to be 5-HT$_{1C}$ mediated (Table 3, [233]). The effects of selective 5-HT reuptake inhibitors have been less extensively studied. One such drug, chlorimipramine [181] reduced mCPP-induced hypothermia after chronic treatment [233] while both chronic sertraline and citalopram reduced mCPP induced hypolocomotion [234]. However, chronic ORG 6997 (Organon) did not affect the rat penile erection model [230]. Noradrenergic reuptake inhibitors do not appear to share these properties. Thus, although imipramine (Ciba-Geigy) [181] reduced hyperthermic

responses to mCPP [233], it potentiated mCPP-induced hypolocomotion [235] and prolactin release but did not affect corticosterone or growth hormone release [236]. Also another noradrenergic reuptake inhibitor, desipramine (Ciba-Geigy) [181], did not alter the hypolocomotor response [229]. The atypical antidepressant iprindole (Wyeth Research) was also without effect after chronic administration [229]. These findings might be caused by altered metabolism or disposition of mCPP, but they suggest that, in rats, treatments that enhance extraneuronal 5-HT levels desensitise 5-HT$_{1C}$ receptor function. This in turn may cause, or contribute to, their antidepressant efficacy. The therapeutic effect of subchronic mCPP [227] could therefore also be explained by 5-HT$_{1C}$ receptor desensitization. Indeed, chronic mCPP desensitises mCPP-induced hypolocomotion [237-239] and changes in cerebral glucose metabolism [238] without altering its pharmacokinetic profile [238,239]. Chronic imipramine treatment is reported to reduce the hyperthermic effects of mCPP in humans [157] and in rats [233].

Table 5: The effects of chronic antidepressant treatments on putative rat models of 5-HT$_{1C}$ receptor functional activity.

Treatment		Paradigm (mCPP-induced)	Effect	Reference
Class	**Drug**			
MAOI	Phenelzine	Hypolocomotion	Decrease	229
	Nialamide	Hypolocomotion	Decrease	229
	Tranylcypromine	Penile erections	Decrease	230
	Chlorgyline	Hypophagia	Decrease	232
		Hyperthermia	Decrease	233
SSRI	Chlorimipramine	Hyperthermia	Decrease	233
	Sertraline	Hypolocomotion	Decrease	234
	Citalopram	Hypolocomotion	Decrease	234
	ORG 6997	Penile erections	-	230
SNRI	Imipramine	Hyperthermia	Decrease	233
	Desipramine	Hypolocomotion	Increase	235
		Hypolocomotion		229
Atypical	Iprindole	Hypolocomotion		229

MAOI: monoamine oxidase inhibitor   SSRI: selective serotonin (5-HT) reuptake inhibitor
SNRI: selective noradrenergic reuptake inhibitor   Atypical: atypical antidepressant

This may suggest that 5-HT$_{1C}$ receptors can be desensitised by this drug or that body temperature is affected by some other mechanism. Whether all these results can be safely interpreted as evidence of 5-HT$_{1C}$ receptor desensitization awaits studies of 5-HT$_{1C}$ receptor binding and PI hydrolysis.

Finally, the specific 5-HT reuptake inhibitor fluoxetine (a racemic mixture) and its (-) isomer have been shown to have some affinity for the 5-HT$_{1C}$ site [240]. Since this is roughly ten-fold less than their affinities for the 5-HT reuptake site it may not explain their antidepressant efficacy. Fluoxetine is metabolised to the long-acting metabolite norfluoxetine. This too has

been found to bind to 5-HT$_{1C}$ receptors, and a patent for its use in feeding disorders, OCD, alcoholism, sleep disorders and migraine has been published [502].

In conclusion, the evidence for a role for 5-HT$_{1C}$ receptors in depressive illness is at present neither wholly consistent nor complete. The therapeutic benefit of ritanserin (and presumably mianserin and cyproheptadine) may be secondary to improved sleep, anti-anxiety and energy restoring properties. Some of these at least may not be 5-HT$_{1C}$ mediated.

Migraine

When mCPP was administered to bulimic patients, migraine-like headaches were reported eight to twelve hours later [241]. This response was correlated with plasma levels of mCPP and was more pronounced in patients with a personal or family history of migraine, an effect confirmed in a recent study of migraine patients [242]. Migraine patients given mCPP had enhanced cortisol and temperature responses [242]. Fozard & Gray [243] have argued that 5-HT$_{1C}$ receptor stimulation might be an important step in the pathogenesis of migraine for two reasons: firstly, mCPP activates 5-HT$_{1C}$ but antagonizes 5-HT$_2$ receptors (see mCPP section). and secondly, methysergide pizotifen, mianserin and cyproheptadine, all of which are non-specific 5-HT$_{1C}$ and 5-HT$_2$ receptor antagonists are clinically effective antimigraine agents, but the selective 5-HT$_2$ antagonist [16] ketanserin is not [244]. Recently Brown et al. [63] have demonstrated that two effective antimigraine agents, ergotamine (Wellcome) and dihydroergotamine (Sandoz), are also potent 5-HT$_{1C}$ agonists but only occasionally induce headaches [245]. However, this may be due to the additional potent 5-HT$_1$-like constrictor activity of these drugs on large dilated cerebral arteries [63], which may confer antimigraine efficacy [245], this action is shared by sumatriptan (Glaxo), a novel antimigraine agent [246]. Since both drugs also activate other receptors (e.g. α adrenoceptors and dopamine receptors) these could conceivably mediate their effects [247]. It could also be argued that the α_1 adrenoceptor blocking activity of ketanserin (Table 1) prevented antimigraine efficacy. The relationship of 5-HT$_{1C}$ receptors to the clinical efficacy of the 5-HT$_{1C}$/5-HT$_2$ receptor antagonists may also be disputed since they too have additional actions. Thus cyproheptadine and pizotifen have similar and appreciable affinities for dopamine, muscarinic cholinergic and α_1 adrenoceptor sites, and lower affinities for α_2 adrenoceptors (Table 1). They also have an affinity for histamine H$_1$ receptors equal to that for 5-HT$_2$ and 5-HT$_{1C}$ sites (Table 1, [15]). Mianserin, too, has affinity for histamine H$_1$ receptors and lower affinity for both α_1 and α_2 adrenoceptors, but has low affinity for dopamine receptors and is inactive at cholinergic receptors (Table 1, [15]). Methysergide, however, has little affinity for histamine, α adrenoceptors or cholinergic receptors (Table 1, [15]). These four drugs, therefore, only share high affinity at the 5-HT$_2$ and 5-HT$_{1C}$ sites, and the lack of clinical efficacy of histamine H$_1$, cholinergic, dopaminergic or α adrenoceptor antagonists [248] suggests that 5-HT$_{1C}$/5-HT$_2$ receptors alone are clinically relevant. The modest antimigraine efficacy of ICI 169,369 [249], another relatively specific 5-HT$_2$ and 5-HT$_{1C}$ receptor antagonist [100,250], may be attributable to the dose used, while the clinical efficacy of chronic administration of 5-HT reuptake inhibitors such as amitriptyline (Merck Sharp & Dohme) [251] and fluoxetine [252,253] as migraine prophylactics may be caused by down-regulation of 5-HT$_{1C}$ receptors (see section on depression and Table 5).

One interesting observation of the migraine-precipitant action of mCPP is the long time interval between administration and headache; peak mCPP concentrations were seen two to three hours after administration [241,242], whereas headache occurred up to twelve hours later.

This suggests an indirect mode of action and may be consistent with the prophylactic but not acute efficacy of 5-HT$_{1C}$/5-HT$_2$ receptor antagonists in migraine [243].

In conclusion, 5-HT$_{1C}$ receptors may be involved in migraine. Further proof awaits the development of more specific compounds and further testing of existing drugs.

Sleep Disorders

In man, the serotonergic system has been considered hypnogenic. Treatments that enhance 5-HT function, such as the administration of the 5-HT precursors tryptophan [254,255,256] or 5-hydroxytryptophan (5-HTP) [256,257], increase either sleep time, the duration of slow wave sleep (SWS) or the duration of rapid eye movement sleep (REMS). Conversely the 5-HT depleter PCPA reduces REMS [258]. In cats, PCPA or 5-HT neurotoxic lesions can lead to total insomnia that can be reversed by 5-HTP [256]. As with many other functions of 5-HT, the recognition of 5-HT receptor subtypes has suggested that 5-HT may have differing effects on sleep depending on which subtype is studied. 5-HT$_{1A}$ receptor agonists, for instance, increase wakefulness in both rats [259,260] and humans [261].

MCPP reduced total sleep time, sleep efficiency, SWS and REMS in two clinical studies [262,263]. Wakefulness was increased and subjective behavioural effects of mCPP seemed more prominent than in patients given mCPP during waking hours [262]. This may reflect the absence of environmental distraction. The effects of mCPP are consistent with reports that the 5-HT reuptake inhibitors zimelidine and indalpine (Groupe Pharmuka) also reduce total sleep time and REMS when given acutely [264]. In rats the mixed 5-HT$_2$/5-HT$_{1C}$ agonist 2,5-dimethoxy-4-methylamphetamine (DOM) (Table 3) reduced both SWS and REMS [265]. The effects of the 5-HT reuptake inhibitor zimeldine are more complex. Initially it is reported to increase wakefulness and reduce REMS but after roughly two hours it enhances SWS [266]. Other 5-HT reuptake inhibitors, such as fluoxetine [267], indalpine [268] and alaproclate (Astra) [269], also reduce REMS and can enhance SWS [267,270]. The biphasic effects of this class of compounds is likely to reflect the stimulation of different 5-HT receptor subtypes by the released 5-HT. The increased wakefulness is unlikely to be 5-HT$_2$ or 5-HT$_{1C}$ receptor mediated as it is not blocked by ritanserin [266]. Curiously, TFMPP given to rats reduced REMS but also increased SWS in the second hour after administration, although this effect was not dose-dependent [267]. The drug's profile of action was thus dissimilar to that of mCPP in humans but similar to 5-HT reuptake inhibitor; its action may therefore be due to 5-HT releasing properties [71].

The effect of drugs with 5-HT$_{1C}$ antagonist properties is clearer. The 5-HT$_2$ and 5-HT$_{1C}$ receptor antagonist, ritanserin, increases SWS, reduces sleep onset latency and improves subjective sleep quality in both young [272-274] and old [275] healthy volunteers. REMS is reduced in some [272,276] but not all [275,277] reports. A shift from early stage SWS to later, deeper SWS stages is generally reported [272,273,275-277]. Ritanserin has also proved efficacious in insomniac patients [278] and patients suffering from dysthymia (depressive neurosis) [277]. The drug achieved these effects acutely [273,275,276,279], chronically [273,275,277] and dose-dependently [276]. Only Adam & Oswald [275] reported withdrawal wakefulness. Other drugs with 5-HT$_{1C}$ antagonist actions such as mianserin [280], cyproheptadine [281,282] and pizotifen [283] have similar effects, but methysergide [284] and metergoline [282] do not. This may reflect the lack of specificity of these compounds (Table 1, [16]) such as their 5-HT$_{1D}$ partial agonist actions [168]. In rats, too, ritanserin increases SWS [265,266,285] although not always significantly [18]. However, some studies suggest that the deepest phase of SWS (SWS2) is increased but total SWS is not [266,285] and not all report

significantly reduced wakefulness [18,266]. As in clinical studies, REMS was reduced [18,265,285] although not universely [266]. Only one study of the effects of two other 5-HT$_2$/5-HT$_{1C}$ receptor antagonists with an otherwise relatively clean profile of action, ICI 169,369 [250] and ICI 170,809 (Table 1), has been published. However while they increased REMS latency, as did ritanserin, ICI 169,369 had no effect and ICI 170,809 had little effect on SWS, although in the same study ritanserin reduced it [286]. Unfortunately SWS in this study was not subdivided into SWS1 and SWS2. Thus both antagonists might have increased SWS2 as seen by others. The effect of ritanserin on all sleep stages can be reversed by the 5-HT$_{1C}$/5-HT$_2$ agonist DOM [287]. Recently the effect on rat sleep patterns of SR 46349B, a relatively selective 5-HT$_2$ receptor antagonist (Table 1) was studied. This drug also reduced REMS and increased REMS latency, as did ritanserin [18]. This suggests that 5-HT$_2$ receptor antagonism mediates this effect. As neither SR 46349B nor ritanserin clearly affected SWS or wakefulness in this study it is not possible to decide whether these functions are 5-HT$_2$ or 5-HT$_{1C}$ receptor mediated [18].

The shift in sleep pattern derived from ritanserin and other 5-HT$_2$/5-HT$_{1C}$ receptor antagonists is subjectively reported to be beneficial and refreshing despite the reduced amount of REM sleep. The effects are also not associated with sedation [272]. Given the largely opposite effects of mCPP it seems possible that 5-HT$_{1C}$ receptors might mediate these actions. Should reduced REMS be caused by 5-HT$_2$ receptor blockade, as suggested by the results of Rinaldo-Carmona et al. [18], and should increased SWS and reduced wakefulness be 5-HT$_{1C}$ receptor mediated, then selective 5-HT$_{1C}$ antagonists could be of particular therapeutic use in the treatment of sleep disorders. Further trials with more selective drugs are awaited.

Feeding Disorders

Administration of mCPP and TFMPP to food-deprived [60,428,430] or freely feeding [205] rats reduces subsequent food, but in the case of mCPP, not water [288] intake. The effect is not secondary to anxiety as it is not reversed by benzodiazepine anxiolytics [88]. Nor is it likely to be secondary to hypolocomotion as, unlike hypophagia, the effect is not blocked by either cyanopindolol or (−)propranolol [60]. Also TFMPP administration into the hypothalamus causes hypophagia only [289]. Since the hypophagia was not blocked by the antiemetic trimethobenzamide, mCPP is unlikely to induce nausea [290]. The accelerated appearance of the postprandial satiety sequence following both mCPP and TFMPP suggests that a satiety mechanism is probably responsible for their hypophagic actions [Kitchener & Dourish, unpublished observations].

The action of mCPP was blocked by the non-selective 5-HT$_2$/5-HT$_{1C}$ receptor blockers metergoline, mianserin, mesulergine and 1-NP but not by the selective 5-HT$_2$ antagonist ketanserin or 5-HT$_3$ antagonist ICS 205,930 (Table 4, [60]). Inhibition of mCPP-induced hypophagia by ten antagonists was found to correlate only with their affinities for the 5-HT$_{1C}$ site [66]. Studies on the pharmacology of TFMPP-induced hypophagia have produced a less clear discrimination between the effects of 5-HT$_{1C}$ and selective 5-HT$_1$ receptor antagonists (Table 3, [430]). MK 212 also reduces feeding in rats [291] but the mechanism of action is unknown. The hypophagic effects of DOI [292] and quipazine (Miles Scientific) [293], both of which have high affinity for the 5-HT$_{1C}$ site [16,26], have been reported to be mediated by 5-HT$_2$ receptors because they are ketanserin sensitive.

This may reflect differences in experimental design but is most likely to be secondary to response competition between feeding and the behavioural effects of 5-HT$_2$ receptor

stimulation, one possibility being hallucination [214]. Indeed DOI, at least, disrupts the postprandial satiety sequence [294] while quipazine reduces water intake also [288].

The effects of 5-HT$_1$/5-HT$_{1C}$ antagonists have also implicated 5-HT$_{1C}$ receptors in the control of food intake. Mianserin, cyproheptadine and 1-NP all increased the food intake of freely feeding rats over four hours as did mesulergine, albeit not significantly [60]. Likewise Dourish *et al.* [295] observed increased food intake after administration of metergoline, methysergide, mianserin and methiothepin. Metergoline, ritanserin and methysergide increased the consumption of palatable wet mash in rats partially sated prior to drug injection [296]. In contrast, the specific 5-HT$_2$ antagonist ketanserin had no effect on food intake in freely feeding rats [59,295]; neither did ritanserin at low doses [295,297] which may not block 5-HT$_{1C}$ receptors [66]. Increased food intake is only seen under conditions of satiety where low rates of feeding occur. Under conditions of high feeding rates none of these drugs was effective [60,296]. This is consistent with mediation by blockade of satiety signals and may explain the contradictory findings of cyproheptadine's hyperphagic actions [298,299]. It is also of interest that the hyperphagic effects of these compounds has only rarely been observed to increase daily food intake or body weight [60,295,300-302], the exceptions being metergoline [295] and high doses of ritanserin [297]. This may suggest the presence of compensatory mechanisms.

In healthy volunteers or bulimics, mCPP has not been reported to affect appetite [303] possibly due to the short nature of most studies which are not designed to elicit changes in appetite. Since mCPP-induced anxiety is seen at doses ten-fold less than those necessary for hypophagia in rats [60,205], the doses used clinically may have been too low. However fenfluramine, a drug that enhances synaptic cleft 5-HT, is a noted, clinically effective anorexic agent [304]. It has been claimed to act via 5-HT$_2$ receptors in rats as it was blocked by ketanserin [305], but this was not confirmed by Neil & Cooper [288]. This group concluded that fenfluramine anorexia was 5-HT$_1$, but not 5-HT$_{1A}$ or 5-HT$_{1B}$, mediated. However they could not block the effects of fenfluramine with the non-specific 5-HT$_2$/5-HT$_{1C}$ receptor antagonist ICI 169,369 (Table 1, [17,100,250]) and only achieved a modest non-significant antagonism with mianserin. Consistent with these results were those of Garattini *et al.* [306], which showed antagonism of fenfluramine by metergoline but not by doses of ritanserin that might be specific for 5-HT$_2$ receptors [66]. However, a firm attribution of fenfluramine's actions (or at least a component of them) to 5-HT$_{1C}$ receptor stimulation is not possible at present, although the drug has considerable affinity for the 5-HT$_{1C}$ receptor [163] and has been reported to cause anorexia in rats pretreated with the 5-HT synthesis inhibitor p-chlorophenylalanine [307]. This suggests that the drug may act directly on postsynaptic 5-HT$_{1C}$ receptors.

A second class of drugs that increase synaptic cleft 5-HT, the specific 5-HT reuptake inhibitors, are also clinically effective anorexic agents [308,309]. Fluoxetine [310-312], paroxetine (SmithKline Beecham) [309], zimelidine (Astra) [313], RU 25591 (Roussel UCLAF) [314] and sertraline [315,316] are hypophagic in rodents. Like fenfluramine the mode of action of these drugs is uncertain. Although the effect of sertraline was blocked by metergoline and methysergide, but not ketanserin [315], fluoxetine was not blocked by metergoline or LY 53857 [317], both of which are non-specific antagonists of 5-HT$_{1C}$ receptors (Table 1). The effect of drugs which enhance extraneuronal 5-HT may be mediated via more than one 5-HT receptor subtype. Thus 5-HT can reduce food intake when injected into the paraventricular nucleus of the hypothalamus [318] or when given peripherally [319]. Both 5-HT$_{1B}$ and 5-HT$_{1C}$ receptors may mediate central hypophagic mechanisms [60,289], while 5-HT$_2$ receptors may mediate them peripherally [297,319,320]. The above evidence shows that the hypophagic actions of treatments which may enhance 5-HT$_{1C}$ receptor function

are not well characterised in species other than rodents. Clinically effective anorectic agents may therefore attain their efficacy via mechanisms other than 5-HT$_{1C}$ receptor stimulation.

Obesity

The hypophagic effects of 5-HT$_{1C}$ receptor stimulation might be applied as an aid to weight loss, particularly where obesity is life threatening, as in those with cardiovascular disease. The 5-HT reuptake inhibitor fluoxetine has been shown to induce weight loss in obese patients [321-323] albeit not of great magnitude. Fenfluramine has long been recognised as an effective anorexic agent [304]. This drug achieves its anorexic response rapidly to give a new body weight set point which is often lost on withdrawal. Since the drug can induce 5-HT lesions [304], albeit at high doses, alternative therapies might well be more acceptable.

Bulimia Nervosa

Another possible indication is Bulimia Nervosa. This disorder is estimated to affect 1.3-10.1% of American women [79] and is characterised by compulsive eating binges followed by self-induced vomiting, laxative abuse, or other methods to prevent weight gain. It can cause serious morbidity and even mortality. Fenfluramine has been claimed to have beneficial effects in bulimics, reducing bingeing [324] in one acute study. A second study observed reduced bingeing within a week of chronic fenfluramine administration [325]. In both studies fenfluramine may have acted by a direct reduction of feeding behaviour, as Blouin et al. [325] reported a reduction in caloric intake in the fenfluramine treated patients. Antidepressants represent a second class of treatment. Thus monoamine oxidase inhibitors such as phenelzine [326] and isocarboxazid (Roche) [327], which would be expected to increase extraneuronal 5-HT levels, are clinically effective. The specific 5-HT reuptake inhibitor fluoxetine is also effective [79,328]. Interestingly so is trazodone [329], which could act via its metabolism to mCPP [56]. The onset of fluoxetine's therapeutic effects is rapid [79] suggesting that, as with fenfluramine, appetite suppression may be involved. This is consistent with the reported relapse of two fluoxetine treated patients when given the 5-HT$_{1C}$/5-HT$_2$ receptor antagonist cyproheptadine [330]. However the noradrenergic reuptake inhibitors [146] imipramine [331], desipramine [332] and nomifensine (Hoechst) [333] are also effective, which could reflect the considerable overlap between depression and bulimia [328]. One antidepressant that was not effective in the treatment of bulimia was mianserin [334]. Since blockade of 5-HT$_{1C}$ receptors by this drug [16] may enhance appetite (see above and the following section) this may not be surprising. However, chronic administration of antidepressants that enhance extraneuronal 5-HT may down-regulate 5-HT$_{1C}$ receptors (see section on depression and Table 5), which could detract from efficacy. The possibility remains that 5-HT$_{1C}$ receptor agonists might be of use in the treatment of Bulimia Nervosa.

Anorexia Nervosa

Clinically the non-specific 5-HT$_{1C}$/5-HT$_2$ antagonists cyproheptadine [301,302,335,336] and pizotifen [337,338] stimulate appetite. Both of these drugs also share a high affinity for histamine receptors (Table 1, [15]). However mianserin, methysergide and metergoline are not reported to increase weight [306,339]. These discrepancies might result from the non-specific nature of the drugs. The effect of the relatively specific 5-HT$_{1C}$/5-HT$_2$ receptor antagonist ritanserin might therefore be more relevant. Out of six large clinical trials with this drug, only one reported mild weight gain as a side effect [223] and this was tolerated after the first month. Another study [131] observed one case of increased appetite in twenty-two patients given 5 mg/kg daily for four weeks but other groups using higher [130,141,221] or similar doses [129] did not. No effects on appetite were reported in several smaller trials [272,275,279].

Furthermore, no alterations in appetite were observed in a study with ICI 169,369 on migraine [249]. One reason for the discrepancy between the effects of cyproheptadine and pizotifen and the studies of ritanserin may be that the latter were not set up to study appetite, which might thus have been overlooked. Alternatively the expected increase in appetite may be mild in most patients.

The above properties suggest that 5-HT$_{1C}$ receptor antagonists might be of use in the treatment of anorexia nervosa. However, to date, no drug has consistently proved effective in this disorder. If appetite stimulation could improve the symptomology of anorexia one would predict that 5-HT$_{1C}$ receptor antagonists or chronic treatment with antidepressants which enhance extraneural 5-HT might prove effective. Since neither the 5-HT$_{1C}$/5-HT$_2$ receptor antagonist cyproheptadine [340,341,342] nor the 5-HT reuptake blocker chlorimipramine [343] had therapeutic value in anorexics, this seems unlikely.

5-HT$_{1C}$ receptors and feeding disorders: Summary

In conclusion 5-HT$_{1C}$ receptor stimulation is very likely to mediate hypophagia. This might suggest therapeutic utility in obesity and in the control of binge eating in bulimics. Unfortunately the anxiogenic properties of 5-HT$_{1C}$ receptor agonists might prove a significant contraindication in the absence of any evidence that 5-HT$_{1C}$ receptor subtypes exist that differentiate between the two actions. The possibility of tolerance to repeated administration of 5-HT$_{1C}$ receptor agonists, as reported by Sills et al. [237], Freo et al. [238] and Ulrichsen et al. [239], might also be a problem. 5-HT$_{1C}$ receptor blockade may produce increased appetite and weight gain. Drugs with these properties could therefore prove useful in the treatment of anorexia nervosa.

Cognition impairment

Although data on the role of 5-HT in learning and memory has been inconsistent, it is generally thought treatments that enhance 5-HT function led to impaired learning and memory [344]. It was therefore surprising when animal studies with 5-HT reuptake inhibitors such as alaproclate, zimeldine [345] and fluoxetine [346,347] observed cognitive enhancement after acute administration. Altman et al. [348], however, reported that the effects of alaproclate and zimeldine were opposed by pretreatment with quipazine, a 5-HT agonist, but not affected by cyproheptadine. They speculated that the effects of 5-HT reuptake inhibitors may be mediated by effects other than enhanced extraneuronal 5-HT [348].

Clinically, a number of studies have reported cognition-enhancing effects of reuptake inhibitors. Thus chronic citalopram (Lundbeck) improved concentration and absent-mindedness in demented patients [349] but this effect was not reproduced in a second larger study [350]. Chronic fluoxetine enhanced memory function in depressive patients in two studies [351,352] but not in a third [353]. However, as depression impairs cognition [351], these effects may be secondary to clinical improvement. Chronic zimeldine attenuated alcohol-induced memory impairment [354] and chronic fluvoxamine was reported to improve memory task performance in patients with alcohol amnesic disorder [355]. In healthy volunteers neither acute [356,357] nor subchronic fluvoxamine had any effect on learning and memory performance [358]. Chronic clomipramine enhanced verbal fluency, the ability to recognise nonsense words and motor function [359], while acute sertraline was considered to induce an 'alerting' response [360]. However in elderly volunteers subchronic fluvoxamine had little effect on psychomotor function [361] as did subchronic treatment with sertraline which, in addition, had no effect in memory tests [362]. The studies seem to suggest that clinically, chronic treatment with this class of drugs is more likely to produce enhanced cognition. This

may therefore be caused by the induction of neurochemical changes such as receptor down-regulation (see section on depression).

MCPP has been administered to Alzheimer's disease patients and produced an elevated anxiety response compared with normal age-matched volunteers at a higher [225] but not at a lower [224] dose. Cognition was also impaired to a greater extent at the higher dose [225] but only the lower dose of mCPP was found to worsen episodic memory of the elderly volunteers [224]. These effects could well be secondary to anxiety or light-headedness/dizziness [84,224,225]. MCPP-induced cortisol and prolactin release was not altered in Alzheimer patients after either low [224] or higher [225] doses.

Drugs with 5-HT$_{1C}$ receptor antagonist properties have been reported to enhance cognitive performance in some animal studies. Thus post-training mianserin, metergoline and methysergide improved memory of mice for an aversive behaviour [363]. Mianserin also attenuated age-induced deficits in passive avoidance retention of rats [264] and protected rats against an hypoxia-induced deficit [347]. These effects are probably 5-HT$_2$ mediated, as the selective 5-HT$_2$ receptor antagonist ketanserin [16] had similar effects in all three models [363,364,367].

Clinically, chronic mianserin tended to impair the performance of both psychomotor and memory tests [358,361,362]. This effect was thought to be secondary to the drug's sedative properties and was less pronounced after several days of treatment. Sedative properties are common to most of the older 5-HT$_{1C}$/5-HT$_2$ receptor antagonists due to their affinity for histamine H$_1$ receptors (Table 1) and was thought to account for the psychomotor retarding effects of acute cyproheptadine, although memory was unaffected in this study [365]. One other such drug, ritanserin, has been reported to enhance motivation and increase subjective energy levels [221]. At present, therefore, there is little evidence to support a role for 5-HT$_{1C}$ receptors in cognition.

Schizophrenia

MCPP has been reported to increase [366-368], have no effect [369], or decrease [370] psychotic symptomology. Blunted ACTH and prolactin responses to mCPP have been reported by Iqbal et al. [368] but were not seen in other studies [366,369,370], although Kahn et al. [370] reported blunted temperature responses to mCPP. Negative symptoms were unaltered by mCPP [366].

Conversely ritanserin has been reported to reduce negative/affective symptoms in schizophrenia (anergia, anxiety/depression, activity, hostility [221,371,372]), as has cyproheptadine [373]. Ritanserin is also reported to reduce neuroleptic-induced extrapyramidal side effects [374] and those induced by the dopamine precursor DOPA in patients with Parkinson's disease [375,376]. Furthermore it may prevent neuroleptic-induced akathesia [377]. These properties are shared by the atypical antipsychotic clozapine, on which basis it is considered to be superior to classical neuroleptic agents [378]. Since, like ritanserin, clozapine has high affinity for 5-HT$_2$ receptors (Table 6, [378]) and an even higher affinity for 5-HT$_{1C}$ sites (Table 6, [379]), these might mediate their actions. Indeed a high affinity for the 5-HT$_{1C}$ receptor is also possessed by several other putative atypical [380] antipsychotic agents including tiospirone (Mead Johnston) [379,380], fluperlapine (Sandoz) [380] and rilapine (Knoll Pharmaceuticals) [380]. However similar efficacy against negative symptoms and neuroleptic-induced extrapyramidal side effects has also been claimed for setoperone [381], risperidone [372] and melperone (Pharmacia) [382-384] while preclinical evidence suggests

that amperozide (Pharmacia) [385-387] is also atypical. All of these drugs have moderate or, in the case of amperozide and melperone, submicromolar affinities for the 5-HT$_{1C}$ site [16,379,380]. Clearly no correlation can exist between 5-HT$_{1C}$ receptor affinity and atypical antipsychotic properties. However, all the above compounds also have considerable affinity for the 5-HT$_2$ receptor [16,379,380] with tiosperone, rilapine, risperidone, setoperone, amperozide and melperone having between twenty- and one hundred and sixty-fold selectivity for the site [16,379,380], although tiosperone was not selective in the study of Canton *et al.* [379]. Hence 5-HT$_2$ receptor antagonism is much more likely to be the determinant of an atypical antipsychotic profile, although this does not account for the absence of such properties from chlorpromazine, spiperone and loxapine – all of which have high affinity for both 5-HT$_2$ and dopamine D$_2$ sites [380]. As 5-HT$_{1C}$ receptors do not seem to be important in the action of antipsychotic drugs the induction of psychotic symptoms by mCPP is either secondary to anxiogenesis or mediated by properties unrelated to 5-HT$_{1C}$ receptors. Such an effect may be observed by the drugs antagonist efficacy at 5-HT$_2$ receptors (Table 2).

Figure 3: Antipsychotic agents

Autism

Autistic disorder is a syndrome originating in early childhood. It affects two to five children in every million, and is characterised by prominent distortions in social, linguistic and cognitive development. Pervasive lack of interest in others, and unresponsiveness to them, are essential features of the disorder.

Autistic children who develop spoken language often exhibit abnormal speech patterns including senseless or compulsive repetition of words heard (echolalia). Motor stereotypes such as hand flapping are common, as are self-abusive behaviours like head banging. Resistance to change is also characteristic. In the 1960s the syndrome was often described as early schizophrenia.

One prominent feature of autism is the presence of elevated plasma levels of 5-HT, which positively correlat with the cognitive, behavioural and motor deficits of subjects [388]. Studies of treatments designed to lower plasma 5-HT levels were therefore initiated. Early studies with fenfluramine, which is known to reduce brain 5-HT levels after chronic administration [389], reported dramatic effects in three autistic children [390]. However later studies have largely

found no effect of the drug on IQ or maladaptive behaviour and only a slight improvement in apparent developmental age [391]. The non-specific 5-HT antagonist, methysergide [16], was also without significant effect [392]. There is thus little evidence to support a role for 5-HT$_{1C}$ receptor ligands in this disorder at the present time.

Table 6: Affinity of typical and atypical antipsychotic drugs for 5-HT$_{1C}$ and 5-HT$_2$ receptors

Compound	pK$_i$ 5-HT$_{1C}$	pK$_i$ 5-HT$_2$	Selectivity for 5-HT$_2$ over 5-HT$_{1C}$	Class
Loxapine	9.4	8.7	4.7	Typical
Clozapine	8.1	8.3	1.4	Atypical
	8.1[a]	7.6[a]	0.3	
Tiosperone	8.0	10.2	153	Atypical
	7.6[a]	8.5[a]	7.9	
Fluperlapine	7.7	8.1	2.3	Atypical
Rilapine	7.6	9.1	29	Atypical
Chlorpromazine	7.6	8.7	13.5	Typical
	7.9[a]	8.1[a]	1.7	
Risperidone	7.5	9.7	160	Atypical
	7.5[a]	9.2[a]	49	
Setoperone	7.3[b]	8.6[b]	20	Atypical
Spiperone	6.0	9.4	2417	Typical
	6.0[a]	8.8[a]	631	
Amperozide	5.9	7.9	100	Atypical
Melperone	5.9	7.5	42	Atypical

All data from [380] except:
[a] Ref [379]   [b] Ref [16]

Pain

5-HT$_{1C}$ receptors have recently been identified in the spinal cord [393]. Iontophoretic administration of mCPP to dorsal horn nociceptive neurons located within the spinal cord is inhibitory [394]. Systemic administration of mCPP and TFMPP to spinal rats dose-dependently inhibited sensitivity to noxious stimuli which induce the ventroflexion withdrawal reflex [395]. This indicates a spinal or subspinal site of action. The pharmacology of these responses has not been investigated but 5-HT$_{1C}$ receptor medication of antinociception was suggested by McKearney et al. [396]. In this study MK 212, mCPP and TFMPP all increase the shock intensity tolerated by monkeys. This effect was blocked by methysergide a non selective 5-HT$_{1C}$ receptor antagonist (Table 1), but not by the selective 5-HT$_2$ receptor blockers ketanserin or pirenperone. Little human data exists, but, in contrast to the above, ritanserin was reported to increase subjective path thresholds [397]. This effect was modest however and might be related to the migraine prophylactic properties of the drug.

Priapism

MCPP, TFMPP or MK 212 administration causes penile erections in rats. MCPP-induced erections were antagonised by the 5-HT antagonists metergoline, cyproheptadine, mesulergine, mianserin and ritanserin (Table 3, [231]) all of which have high affinity for the $5-HT_{1C}$ site [16]. The 50% inhibitory dose (ID_{50}) values of these drugs were higher than their equivalents against mCPP-induced hypophagia [66] but the rank order of potency was consistent in both paradigms. Ketanserin, the selective $5-HT_2$ antagonist [16], also antagonised mCPP-induced penile erections but only at a relatively high dose [231] consistent with its weak affinity at the $5-HT_{1C}$ site [16] and its rank order of potency against mCPP-induced hypophagia [66]. The more selective $5-HT_2$ receptor antagonist spiperone [16] was inactive [231]. Interestingly, the non-specific $5-HT_2/5-HT_{1C}$ agonist DOI (Table 3) only induced penile erections in the presence of specific $5-HT_2$ receptor antagonists [231] suggesting an interaction between the two sites. MCPP also induced penile erection in rhesus monkeys which was blocked by metergoline [398]. The effect of mCPP may be mediated centrally as penile erections are seen in the rat after intraventricular administration of the 5-HT releasing agent fenfluramine [399], and the 5-HT precursor 5-hydroxytryptophan (5-HTP) is only effective when given with the peripheral decarboxylase inhibitor benserazide (Roche) [400].

In humans, priapism is a major disorder affecting ten million Americans [401]. Penile erection is caused by pooling of blood in the penile blood vessels. In priapism, prolonged stagnation of the pooled blood leads to a fall in oxygen content which increases its viscosity and results in fibrosis and impotence [402]. The condition is therefore considered a urological emergency. 30-50% of cases are drug induced, the most common agents being phenothiazines, butyrophenones, hypnotics (e.g. methaqualone), antihypertensives (eg phenoxybenzamine (SmithKline Beecham), prazosin (Pfizer), hydralazine), anticoagulants (heparin, warfarin) and miscellaneous agents such as ethanol, cannabis, phentolamine (Geigy) and testosterone [402]. Antidepressant therapy is also commonly associated with priapism, most notably with monoamine oxidase inhibitors such as phenelzine and the atypical antidepressant trazodone [402]. Since mCPP is a prominent metabolite of trazodone [56] this may explain its association with priapism, although this has not been reported as a consequence of mCPP administration to man [303]. MAOIs could act in a similar way by potentiating extracellular 5-HT. This may suggest a role for $5-HT_{1C}$ receptor antagonists in the prophylactic or acute treatment of this disorder, at least where caused by antidepressants.
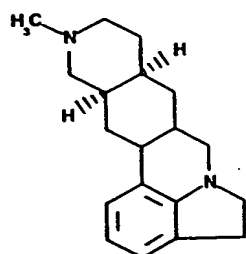
Altered intracranial pressure

The choroid plexus is the major site of formation of cerebral spinal fluid (CSF) in the brain [403,404]. Evidence suggests that 5-HT may control production of CSF, since administration of 5-HT and its precursor 5-HTP [405,406] are inhibitory. 5-HT may reach the choroid plexus from plasma, although concentrations are normally very low [407], or from mast cells found there [408,409]. Evidence also suggests direct serotonergic innervation. Thus moskowitz et al. [410] observed the presence of 5-HT that was sensitive to lesions of the raphe nuclei, the site of serotonergic neuronal cell bodies. Using a fluorescence technique that detected indoleamines, Napoleone et al. [411] reported that 5-HT neurons were located in the walls of the choroid blood vessels and were also sensitive to raphe cell body lesions. However not all studies have observed 5-HT innervation [412,413]. As has already been described (see above) the choroid plexus contains by far the highest concentration of $5-HT_{1C}$ receptors in any part of the body. It therefore seems likely that they mediate serotonergic control of CSF production as first suggested by Pazos et al. [6]. A recent study has shown that SCH 23390 (Schering Plough), a $5-HT_{1C}$ partial agonist [26,414] and dopamine D_1 antagonist [415], markedly
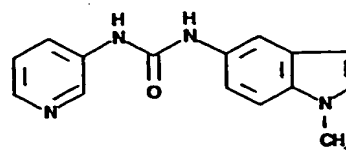
reduces CSF production in rats [416]. Since dopamine D_1 sites are not found in the choroid plexus [415] this effect is probably 5-HT$_{1C}$ receptor mediated. These findings therefore suggest that 5-HT$_{1C}$ receptor agonists may be of use in the treatment of patients with increased intracranial pressure such as those with mass lesions, head trauma, acute or hydrocephalus, or pseudotumour cerebri.

Conclusion

5-HT$_{1C}$ receptor antagonists may have therapeutic applications in a number of areas. This possibility rests principally on the reported effects of the putative 5-HT$_{1C}$ receptor agonist mCPP and of the non-specific 5-HT$_2$/5-HT$_{1C}$ receptor antagonists ritanserin and mianserin as opposed to those of the selective 5-HT$_2$ receptor antagonist ketanserin. Unfortunately ketanserin is not entirely selective, possessing significant affinity for α_1 adrenergic receptors [250], a problem also seen with the newer selective 5-HT$_2$ receptor antagonist RP 62203 (Rhone Poulenc) [17]. Spiperone, which has proved of great value in defining 5-HT$_{1C}$ functions *in vitro* due to its one thousand-fold selectivity for the 5-HT$_2$ site, is of little use *in vivo* because of its dopamine D_2 receptor antagonist properties. Similarly cisapride (Janssen) has one thousand-fold selectivity for the 5-HT$_2$ site but is also a potent 5-HT$_3$ antagonist and 5-HT$_4$ agonist [417]. Clarification of the therapeutic potential of 5-HT$_{1C}$ receptor modulation should be considerably advanced by the recent development of selective 5-HT$_{1C}$ receptor antagonists by both SmithKline Beecham [500] and Sandoz [501] (Figure 4) and the selective 5-HT$_2$ receptor antagonists RP 62203 [17] and MDL 101151 and its (+) isomer MDL 100907 which both have two hundred- to five hundred-fold selectivity for the 5-HT$_2$ site [418]. However it is also dependent on the pharmacological arguments advanced above, which are principally the result of animal data, being equally valid in humans. This cannot be taken for granted as mesulergine has fifty-fold lower affinity for the human than for the rat 5-HT$_2$ receptor. Thus in humans the drug would have selectivity for the 5-HT$_{1C}$ site [21]. The probability that at least some of the above findings may be attributable to the action of drugs at the rat stomach fundus receptor (see section on receptor distribution), should it be found in human central tissue, cannot be excluded, despite preliminary evidence to the contrary [53,54]. In particular mCPP acts as a weak partial agonist of the rat stomach fundus [48,419] while most 5-HT$_2$/5-HT$_{1C}$ receptor antagonists, but not specific 5-HT$_2$ receptor antagonists, are also antagonists of this site [48]. However current evidence strongly favours a therapeutic role for 5-HT$_{1C}$ receptor ligands in at least some of the indications advanced in this review. Chronic treatment with selective 5-HT reuptake inhibitors is the current therapy of choice in many of these indications (OCD, alcoholism, depression, bulimia) and may become more widely used in others (panic disorder, obesity, migraine). Fluoxetine, the most widely studied drug in this class, is associated with significant side effects (insomnia, nausea, asthenia, tremor and sweating) [79] and may be associated with heightened risk of suicide in depressives [421-423] although these effects have not been reported for other 5-HT reuptake inhibitors. Furthermore, the reuptake inhibitors all require two or more weeks administration for effect. Should down regulation of 5-HT$_{1C}$ receptors be their mode of action, the magnitude of this effect is unlikely to be as pronounced as that caused by an antagonist. Specific 5-HT$_{1C}$ ligands may therefore offer advantages both in the speed of onset of action, efficacy, and side effect profile. Finally, it is conceivable that subtypes of the 5-HT$_{1C}$ receptor may exist, although, with the exception of the rat stomach fundus receptor, there is no evidence of this at present. This might allow differentiation of the anxiogenic and other properties of 5-HT$_{1C}$ receptor agonists facilitating their clinical use.

Sandoz

200646A

SmithKline Beecham

Figure 4: Novel selective 5-HT$_{1C}$ receptor antatagonists

Acknowledgements

References

• = of interest   •• = of considerable interest

1. PEROUTKA SJ, SNYDER SH: **Multiple serotonin receptors: differential binding of [³H]5-hydroxytryptamine, [³H]lysergic acid diethylamide and (³H) spiroperidol.** *Mol. Pharmacol.* (1979) 16:687 -699.

2. PEDIGO NW, YAMAMURA HI, NELSON DL: **Discrimination of multiple [³H] 5-hydroxytryptamine-binding sites by the neuroleptic spiperone in rat brain.** *J. Neurochem.* (1981) 36:220-226.

3. MIDDLEMISS DN, FOZARD RJ: **8-hydroxy-2-(di-n-propylamino)tetralin discriminates between subtypes of the 5-HT₁ recognition site.** *Eur. J. Pharmacol.* (1983) 90:151-153.

4. GOZLAN H, EL MESTIKAWAY S, PICHAT L, GLOWINSKI J, HAMON M: **Identification of presynaptic serotonin autoreceptors by a new ligand: [³H]-PAT.** *Nature (London)* (1983) 305:140-142.

5. HOYER D, ENGEL G, KALKMAN HO: **Molecular pharmacology of 5-HT₁ and 5-HT₂ recognition sites in rat and pig brain membranes: radioligand binding studies with [³H]5-HT, [³H]8-OH-DPAT, (-)[¹²⁵I]iodocyanopindolol, [³H] mesulergine and [³H]ketanserin.** *Eur. J. Pharmacol.* (1985) 118:13-23.

6. PAZOS A, HOYER D, PALACIOS JM: **The binding of
•• serotonergic ligands to the porcine choroid plexus: characterization of a new type of serotonin recognition site.** *Eur. J. Pharmacol.* (1984) 106:539-546.
First identification of the 5-HT₁C receptor

7. HEURING RE, PEROUTKA SJ: **Characterization of a novel [³H]5-hydroxytryptamine binding site subtype in bovine brain membranes.** *J. Neurosci.* (1987) 7:894-903.

8. LEONHARDT S, HERRICK-DAVIS K, TITELER M: **Detection of a novel serotonin receptor subtype (5-HT₁E) in human brain: interaction with a GTP-binding protein.** *J. Neurochem.* (1989) 53:465-471.

9. RICHARDSON BP, ENGEL G, DONATSCH P, STADLER PA: **Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs.** *Nature (London)* (1985) 316:126-131.

10. KILPATRICK GJ, JONES BJ, TYERS MB: **The identification and distribution of 5-HT₃ receptors in rat brain using radioligand binding.** *Nature (London)* (1987) 330;746-748.

11. DUMUIS A, BOUHELAL R, SEBBEN M, CORY R, BOCKAERT JA: **A non-classical 5-hydroxytryptamine receptor positively coupled to adenylate cyclase in the central nervous system.** *Mol. Pharmacol.* (1988) 34:880-887.

12. YOUNG WS, KUHAR MJ: **Serotonin receptor localization in rat brain by light microscopic autoradiography.** *Eur. J. Pharmacol.* (1980) 63:237-243.

13. CLOSSE A: **[³H]mesulergine, a selective ligand for serotonin-2 receptors.** *Life Sci.* (1983) 32:2485-2495.

14. LEYSEN JE, NIEMEGEERS CJE, VAN NUETON JM, LADURON PM: **[³H]ketanserin (R41 468), a selective ³H-ligand for serotonin 2 receptor binding sites.** *Mol. Pharmacol.* (1982) 21:301-314.

15. LEYSEN JE, AWOUTERS F, KENNIS L, LADURON PM, VANDENBERK J, JANSSEN PAJ: **Receptor binding profile of R41,468, a novel antagonist of 5-HT₂ receptors.** *Life Sci.* (1981) 28:1015-1022.

16. HOYER D: 5-Hydroxytryptamine receptors and
   • effector coupling mechanisms in peripheral
   tissues. In: Fozard J. (ed). Peripheral actions of 5-
   HT. Oxford University Press, Oxford (1989) pp 72-
   99.
A good review of compound selectivity for 5-HT receptor
subtypes.

17. DOBLE A, GIRDLESTONE D, PIOT O, ALLAM D,
   BETSCHART J, BOIREAU A, DUPUY A, GUEREMY C,
   MENAGER J, ZUNDEL JL, BLANCHARD JC:
   Pharmacological characterization of RP 62203,
   a novel 5- hydroxytryptamine 5-HT$_2$ receptor
   antagonist. Brit. J. Pharmacol. (1992) 106:7-36.

18. RINALDI-CARMONA M, LONGY C, SANTUCCI J, SIMIAND
   J, GAUTRET B, NELIAT G, LABEEUW B, LE FUR G,
   SOUBRIE P, BRELIERE JC: Biochemical and
   pharmacological properties of SR 46349B, a
   new potent and selective 5-hydroxytryptamine
   receptor antagonist. J. Pharm. Exp. Ther. (1992)
   262:759-768.

19. GLENNON RA, BARTYZEL P, TEITLER M: Binding of
   benz[e]- and benz[g]-fused tryptamine
   derivatives at serotonin receptors: Evidence for
   a region of bulk tolerance. (1992) (in Press).

20. HOYER D, PAZOS A, PROBST A, PALACIOS JM:
   Serotonin receptors in the human brain. II.
   Characterization and autoradiographic
   localization of 5-HT$_{1C}$ and 5-HT$_2$ recognition
   sites. Brain Res. (1986) 376:97-107.

21. KAO H-T, ADHAM N, OLSEN MA, WEINSHANK RC,
   BRANCHEK TA, HARTIG PR: Site-directed
   mutagenesis of a single residue changes the
   binding properties of the serotonin 5-HT$_2$
   receptor from a human to a rat pharmacology.
   FEBS Lett. (1992) 307:324-328.

22. PALACIOS JM, MARKSTEIN R, PAZOS A: Serotonin-1C
   sites in the choroid plexus are not linked in a
   stimulatory or inhibitory way to adenylate
   cyclase. Brain Res. (1986) 380:151-154.

23. CONN CJ, SANDERS-BUSH E, HOFFMAN BJ, HARTIG PR:
   •• A unique serotonin receptor in choroid plexus
   is linked to phosphatidylinositol turnover.
   Proc. Natl. Acad. Sci. USA (1986) 83:4086-4088.
First evidence that the 5-HT$_{1C}$ receptor acts through
phosphatidylinositol hydrolysis.

24. BERRIDGE MJ, IRVINE RF: Inositol triphosphate, a
   novel second messenger in cellular signal
   transduction. Nature (London) (1984) 312:315-
   321.

25. NISHIKUZA Y: The role of protein kinase C in cell
   surface signal transduction and tumour
   promotion. Nature (London) (1984) 308:693-698.

26. HOYER D, WAEBER C, SCHOEFFTER P, PALACIOS JM,
   DRAVID A: 5-HT$_{1C}$ receptor-mediated stimulation
   of inositol phosphate production in pig
   choroid plexus. A pharmacological
   characterization. Naunyn-Schmiedeberg's Arch.
   Pharmacol. (1989) 339:252-258.

27. GUNDERSON CB, MILEDI R, PARKER I: Messenger
   RNA from human brain induces drug- and
   voltage-operated channels in Xenopus oocytes.

Nature (London) (1984) 308:421-424.

28. LUBBERT H, HOFFMAN BJ, SNUTCH TP, VAN DYKLE T,
   LEVINE AJ, HARTIG PR, LESTER HA, DAVIDSON N:
   cDNA cloning of a serotonin 5-HT$_{1C}$ receptor
   by electrophysiological assays of mRNA-
   injected Xenopus oocytes. Proc. Natl. Acad. Sci.
   USA (1987) 84:4332-4336.

29. LUBBERT H, SNUTCH TP, DASCAL N, LESTER HA,
   •• DAVIDSON N: Rat brain 5-HT$_{1C}$ receptors are
   encoded by a 5-6 kbase mRNA size class and
   are functionally expressed in injected Xenopus
   oocytes. J. Neurosci. (1987) 7:1159-1165.
Identification of the 5-HT$_{1C}$ receptor mRNA.

30. TAKAHASHI T, NEHER E, SAKMAN B: Rat brain
   serotonin receptors in Xenopus oocytes are
   coupled to endogenous channels. Proc. Natl.
   Acad. Sci. USA (1987) 84:5063-5067.

31. DASCAL N, IFUNE C, HOPKINS R, SNUTCH TP, LUBBERT
   H, DAVIDSON N, SIMON MI, LESTER HA:
   Involvement of a GTP-binding protein in
   mediation of serotonin and acetylcholine
   responses in Xenopus oocytes injected with rat
   brain messenger RNA. Mol. Brain Res. (1986)
   1:201-209.

32. AOSHIMA H, IIO H, ANAN M, KOBAYASHI S:
   Induction of muscarinic acetylcholine,
   serotonin and substance P receptors in
   Xenopus oocytes injected with mRNA prepared
   from the small intestine of rats. Mol. Brain Res.
   (1990) 2:15-27.

33. PANICKER MM, PARKER I, MILEDI R: Receptors of the
   serotonin 1C subtype expressed from cloned
   DNA mediate the closing of K$^+$ membrane
   channels encoded by brain mRNA. Proc. Natl.
   Acad. Sci. USA (1991) 88:2560-2562.

34. GUNDERSON CB, MILEDI R, PARKER I: Serotonin
   receptors expressed by brain mRNA in
   Xenopus oocytes mediate three different ionic
   currents. J. Physiol. (London) (1987) 38683P.

35. PARKER I, PANICKER MM, MILEDI R: Serotonin
   receptors expressed in Xenopus oocytes by
   mRNA from brain mediate a closing of K$^+$
   membrane channels. Mol. Brain Res. (1990) 7:31-
   38.

36. JULIUS D, MACDERMOTT AB, AXEL R, JESSELL TM:
   •• Molecular characterization of a functional
   cDNA encoding the serotonin 1C receptor.
   Science (1988) 241:558-564.
Identification of the 5-HT$_{1C}$ receptor cDNA and amino acid
sequence.

37. SHIH JC, YANG W, CHEN K, GALLAGHER T:
   Molecular biology of serotonin (5-HT)
   receptors. Pharmacol. Biochem. Behav. (1991),
   40:1053-1058.

38. YU L, NGUYEN H, LE H, BLOEM LJ, KOZAK CA,
   HOFFMAN BJ, SNUTCH TP, LESTER HA, DAVIDSON N,
   LUBERT H: The mouse 5-HT$_{1C}$ receptor contains
   eight hydrophobic domains and is X-linked.
   Mol. Brain Res. (1991) 11:143-149.

39. SALTZMAN AG, MORSE B, WHITMAN MM,
   IVANSCHENKO Y, JAYE M, FELDER S: Cloning of the

human serotonin 5-HT$_2$ and 5-HT$_{1C}$ receptor subtypes. *Biochem. Biophys. Res. Commun.* (1991) 181:1469-1478.

40. PRITCHETT DB, BACH AWJ, WOZNY M, TALEB O, DAL
• TOSO R, SHIH JC, SEEBURG PH: Structure and functional expression of cloned rat serotonin 5-HT$_2$ receptor. *EMBO J.* (1988) 7:4135-4140.
5-HT2 receptor cDNA and amino acid sequence characterized.

41. JARZAB B, DOHLER KD: Serotonergic influences on sexual differentiation of the rat brain. *Prog. Brain Res.* (1984) 61:119-126.

42. PAZOS A, PALACIOS JM: Quantitative
•• autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. *Brain Res.* (1985) 346:205-230.
First detailed evidence of the 5-HT$_{1C}$ receptor distribution in central tissue.

43. MENGOD G, NGUYEN H, LE H, WAEBER C, LUBBERT H, PALACIOS JM: The distribution and cellular localization of the serotonin 1C receptor mRNA in the rodent brain examined by in situ hybridization histochemistry. Comparison with receptor binding distribution. *Neuroscience* (1990) 35:577-591.

44. PAZOS A, PROBST A, PALACIOS JM: Serotonin receptors in the human brain-III. Autoradiographic mapping of serotonin-1 receptors. *Neuroscience* (1987) 21:97-112.

45. HOFFMAN BJ, MEZEY E: Distribution of serotonin
•• 5-HT$_{1C}$ receptor mRNA in adult rat brain. *FEBS Lett.* (1989) 247:453-462.
5-HT$_{1C}$ mRNA distribution in central tissue reported.

46. MOLINEAUX SM, JESSEL TM, AXEL R, JULIUS D: 5-HT$_{1C}$ receptor is a prominent serotonin receptor subtype in the central nervous system. *Proc. Natl. Acad. Sci. USA* (1989) 86:6793-6797.

47. BUCHEIT KH, ENGEL G, HAGENBACH A, HOYER D, KALKMAN HO, SEILER MP: The rat isolated stomach fundus strip, a model for 5-HT$_{1C}$ receptors. *Brit. J. Pharmacol.* (1986) 88:367P.

48. CLINESCHMIDT BV, REISS DR, PETTIBONE DJ, ROBINSON JL: Characterization of 5-hydroxytryptamine receptors in rat stomach fundus. *J. Pharmacol. Exper. Ther.* (1985) 235:696-708.

49. COHEN ML, WITTENAUER LA: Relationship between serotonin and tryptamine receptors in the rat stomach fundus. *J. Pharmacol. Exp. Ther.* (1985) 233;7579.

50. COHEN ML, WITTENAUER LA: Serotonin receptor activation of phosphoinositide turnover in uterine, fundal, vascular and tracheal smooth muscle. *J. Cardiovasc. Res.* (1987) 10:176-181.

51. BAEZ M, YU L, COHEN ML: Pharmacological and molecular evidence that the contractile response to serotonin in rat stomach fundus is not mediated by activation of the 5-hydroxytryptamine 1C receptor. *Molec. Pharmacol.* (1990)38:31-37.

52. HARTS J. LIU J, KURSAR JD, BAEZ M, NELSON ML, COHEN ML, YU L: Serotonin inhibition of cyclic AMP formation in Xenopus oocytes injected with rat stomach fundus RNA. *Am. Soc. Neurosci. Abstr.* (1991) 17:113.7.

53. FOQUET M, NGUYEN H, LE H, LUBBERT H: Structure
•• of the mouse 5-HT$_{1C}$, 5-HT$_2$ and stomach fundus serotonin receptor. *Neuroreport* (1992) 3:345-348.
Rat stomach fundus (5-HT$_{2B}$) receptor cDNA and amino acid sequence. identified.

54. FOQUET M, HOYER D, PARDO LA, PAREKH A, KLUXEN FW, KALKMAN HO, STUHMER W, LUBBERT H: Cloning and functional characterization of the rat stomach fundus serotonin receptor. *EMBO J.* (1992) 11:34381-3487.

55. BERENDSEN HHG, JENCK F, BROEKKAMP CLE: Involvement of 5-HT$_{1C}$ receptors in drug-induced penile erections in rats. *Psychopharmacology* (1990) 101:57-61.

56. CACCIA S, BALLABIO M, SAMANIN R, ZANINI MG, GARATTINI S: mCPP, a central 5-HT agonist, is a metabolite of trazodone. *J. Pharm. Pharmacol.* (1981) 33:477-478.

57. MARTIN LL, SANDERS-BUSH E: The serotonin autoreceptor: Antagonism by quipazine. *Neuropharmacology* (1982) 21:445-450.

58. SILLS MA, WOLFE BB, FRAZER A: Determination of selective and non-selective compounds for the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes in rat frontal cortex. *J. Pharmacol. Exp. Therap.* (1984) 231:480-487.

59. KENNETT GA, CURZON G: Evidence that mCPP
•• may have behavioural effects mediated by 5-HT$_{1C}$ receptors. *Brit. J. Pharmacol.* (1988) 94:137-147.
First report of mCPP's 5-HT$_{1C}$ agonist properties in vivo and behavioural consequences.

60. KENNETT GA, CURZON G: Evidence that
•• hypophagia induced by mCPP and TFMPP requires 5-HT$_{1C}$ and 5-HT$_{1B}$ receptors; hypophagia induced by RU 24969 only requires 5-HT$_{1B}$ receptors. *Psychopharmacology* (1988) 95:93-100.
First report that 5-HT$_{1C}$ receptor activation had anorexic effects while blockade was hyperphagic.

61. CONN PJ, SANDERS-BUSH E: Relative efficacies of
•• piperazines at the phosphoinositide hydrolysis-linked serotonergic (5-HT$_2$ and 5-HT$_{1C}$) receptors. *J. Pharmacol. Exp. Therap.* (1987) 242:552-557.
First report of that mCPP was a 5-HT$_{1C}$ receptor agonist in vitro.

62. SCHOEFFTER P, HOYER D: Interactions of arylpiperazines with 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$ and 5-HT$_{1D}$ receptors: do discriminatory 5HT$_{1B}$ receptor ligand exist? *Naunyn Schmeidebergs Arch. Pharmacol.* (1989) 339:675-683.

63. BROWN AM, PATCH TL, KAUMANN AJ: The antimigraine drugs ergotamine and dihydroergotamine are potent 5-HT$_{1C}$ receptor

agonists in piglet choroid plexus. *Br. J. Pharmacol.* (1991) **104**:45-48.

64. SANDERS-BUSH E, BREEDING M: Serotonin 5-HT$_{1C}$ receptor reserve in choroid plexus masks receptor subsensitivity. *J. Pharmacol. Exp. Therap.* (1990) **252**:984-988.

65. SIMANSKY KJ, SCHECHTER LE: Dissociation of behavioural properties of 1-arylpiperazines in models for central serotonergic stimulation in rodents. *Fed. Proc.* (1987) **46**:966.

66. KENNETT GA, CURZON G: Potencies of antagonists indicate that 5-HT$_{1C}$ receptors mediate 1-2(chlorophenyl)piperazine-induced hypophagia. *Brit. J. Pharmacol.* (1991) **103**:2016-2020.

67. COHEN ML, FULLER RW: Anatagonism of vascular serotonin receptors by m-chlorophenylpiperazine and m-trifluorophenylpiperazine. *Life Sci.* (1983) **32**:711-718.

68. ROBERTSON DW, BLOOMQUIST W, WONG DT, COHEN ML: MCPP but not TFMPP is an antagonist at cardiac 5-HT$_3$ receptors. *Life Sci.* (1992) **50**:599-605.

69. HARTIG PR, BRANCHEK TA, WEINSHANK RL: A subfamily of 5-HT$_{1D}$ receptor genes. *Trends in Pharmacological Sciences* (1992) **13**:152-159.

70. SMITH TM, SUCKOW RF: Trazodone and m-chlorophenylpiperazine. Concentration in the brain and receptor activity in the regions associated with anxiety. *Neuropharmacology* (1985) **24**:1067-1071.

71. PETTIBONE DJ, WILLIAMS M: Serotonin-releasing
• effects of substituted piperazines *in vitro*. *Biochem. Pharmacol.* (1984) **33**:1531-1535.
Evidence of 5-HT releasing properties of mCPP.

72. HAMIK A, PEROUTKA SJ: 1-(m-Chlorophenyl)-piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. *Biol. Psychiat.* (1989) **25**:569-575.

73. MARKS J: The benzodiazepines use, overuse, misuse, abuse. Marks J. (ed). MTP Press Ltd, Lancaster (1985) pp 33-38.

74. SALZMAN L, THALER FH: Obsessive compulsive disorder: a review of the literature. *Am. J. Psychiat* (1981) **138**:286-296.

75. ZOHAR J, INSEL TR: Obsessive compulsive disorder: Psychobiological approaches to diagnosis, treatment, and pathophysiology. *Biol. Psychiat* (1987) **22**:667-687.

76. EVANS L, KENARDY J, SCHNEIDER P, HOEY H: Effect of a selective serotonin uptake inhibitor in agorophobia with panic attacks. *Acta Psychiat. Scand.* (1986) **73**:49-53.

77. GORMAN JM, LIEBOWITZ MR, FYER AJ, GOETZ D, CAMPEAS RB, FYER MA, DAVIEA SO, KLEIN DF: An open trial of fluoxetine in the treatment of panic disorder. *J. Clin. Psychopharmacol.* (1987) **7**:329-332.

78. SCHNEIER FR, LIEBOWITZ MR, DAVIES SO, FAIRBANKS J, HOLLANDER E, CAMPEAS R, KLEIN DF: Fluoxetine

in panic disorder. *J. Clin. Psychopharmacol.* (1990) **10**:119-121.

79. LEVINE LR, POPE HG, ENAS GG, WILSON MG, BALLENER JC, *et al.*: Fluoxetine in the treatment of Bulimia Nervosa. A multicenter, placebo-controlled, double-blind trial. *Arch. Gen. Psychiat,* (192) **49**:139-147.

80. MUELLER EA, MURPHY DL, SUNDERLAND T:
•• Neuroendocrine effects of m-chlorophenylpiperazine, a serotonin agonist, in humans. *J. Clin. Endocrinol. Metab.* (1985) **61**:1179-1184.
First report of mCPP's anxiogenic effects in man.

81. CHARNEY DS, WOODS SW, GOODMAN WK, HENINGER
• GR: Serotonin function in anxiety. II. Effects of the serotonin agonist mCPP in panic disorder patients and healthy subjects. *Psychopharmacology* (1987) **92**:14-24.
MCPP reported to induce panic attacks in panic disorder patients.

82. ZOHAR J, MUELLER EA, INSEL TR, ZOHAR-KADOUCH RC, MURPHY DL: Serotonergic responsivity in obsessive compulsive disorder: comparison of patients and healthy controls. *Arch. Gen. Psychiat.* (1987) **44**:946-951.

83. SEIBYL JP, KRYSTAL JH, PRICE LH, WOODS SW,
•• D'AMICO CD, HENINGER GR, CHARNEY DS: Effects of ritanserin on the behavioural neuroendocrine and cardiovascular responses to meta chlorophenylpiperazine in healthy subjects. *Psychiatry Res.* (1991) **38**:227-236.
Blockade of mCPP-induce anxiety by the non-selective 5-HT$_{1C/2}$ receptor antagonist ritanserin.

84. KAHN RS, WETZLER S, ASNIS GM, KLING MA, SUCKOW
• RF, VAN PRAAG HM: Effects of m-chlorophenylpiperazine in normal subjects: a dose response study. *Psychopharmacology* (1990) **100**:339-344.
Report of panic attacks in normal volunteers.

85. KALUS O, KAHN RS, WETZLER S, ASNIS GM, VAN PRAAG HM: Behavioural hypersensitivity to m-chlorophenylpiperazine in a subject with subclinical panic attacks. *Biol. Psychiat.* (1990) **28**:1053-1057.

86. MURPHY DL, MUELLER EA, HILL JL, TOLLIVER TJ, JACOBSEN FM: Comparative anxiogenic, neuroendocrine and other physiologic effects of m-chlorophenylpiperazine given intravenously or orally to healthy volunteers. *Psychopharmacology* (1989) **98**:275-282.

87. MUELLER EA, MURPHY DL, SUNDERLAND T: Further studies of the putative serotonin agonist, m-chlorophenylpiperazine: Evidence for a serotonin receptor mediated mechanism of action in humans. *Psychopharmacology* (1986) **89**:388-391.

88. KENNETT GA, WHITTON P, SHAH K, CURZON G:
•• Anxiogenic-like effects of mCPP and TFMPP in animal models are opposed by 5-HT$_{1C}$ receptor antagonists. *Eur. J. Pharmacol.* (1989) **164**:445-454.
First evidence that 5-HT$_{1C}$ receptors may mediate mCPP-induced anxiogenesis.

89. WHITTON P, CURZON G: Anxiogenic-like effects of infusing 1-(3-chlorophenyl)piperazine (mCPP) into the hippocampus. Psychopharmacology (1990) 100:138-140.
Evidence that one site at which mCPP causes anxiety in rats is the hippocampus.

90. GLEESON S, AHLERS ST, MANSBACH RS, ROUST JM, BARRETT JE: Behavioural studies with anxiolytic drugs. IV. Effects on punished responding of drugs interacting with serotonin receptor subtypes. J. Pharmcol. Exp. Therap. (1989) 250:809-817.

91. KILTS CD, COMMISSARIS RL, CORDON JJ, RECH RH: Lack of central 5-hydroxytryptamine influence on the anticonflict activity of diazepam. Psychopharmacology (1992) 156:375-383.

92. MANSBACH RS, GEYER MA: Blockade of potentiated startle responding in rats by 5-hydroxytryptamine 1A receptor ligands. Eur. J. Pharmacol. (1988) 156:373-383.

93. KENNETT GA, BLACKBURN TP: Anxiolytic-like actions of BRL 46470 - a novel 5-HT₃ antagonist. J. Psychopharmacol. (1990) 4:4.

94. THOMAS DR, NELSON DR, BLACKBURN TP, WOOD MD: BRL 46470: a novel 5-HT₃ receptor antagonist. J. Psychopharmacol. (1990) 4:2.

95. JONES BJ, COSTALL B, DOMENEY AM, KELLY ME, NAYLOR RJ, OAKLEY NR, TYERS MB: The potential anxiolytic activity of GR 38032F, a 5-HT₃-receptor antagonist. Brit. J. Pharmacol. (1988) 93:985-993.

96. PIGGOTT TA, ZOHAR J, HILL JL, BERNSTEIN SE, GROVER GN, ZOHAR- KADOUCH RC, MURPHY DL: Metergoline blocks the behavioural and neuroendocrine effects of orally administered m- chlorophenylpiperazine in patients with obsessive-compulsive disorder. Biol. Psychiat. (1991), 29:418-426.

97. KAHN RS, KALUS O, WETZLER S, CAHN W, ASNIS GM, VAN PRAAG HM: Effects of serotonin antagonists on m-chlorophenylpiperazine- mediated responses in normal subjects. Psychiatry Res. (1990) 33:189-198.

98. KENNETT GA: 5-HT₁c receptor antagonists have anxiolytic-like actions in the rat social interaction model. Psychopharmacology (1992) 107:379-384.
Study suggesting that 5-HT₁c receptor antagonists may have anxiolytic properties.

99. KENNETT GA, PITTAWAY K, BLACKBURN TP: Evidence that 5-HT₁c receptor antagonists are anxiolytic in the Geller-Seifter model of anxiety. Psychopharmacology (1993) Submitted.

100. HOYER D: Competitive antagonism by recognised 5-HT₂-receptor antagonists at 5-HT₁c receptors. Naunyn-Schmiedebergs Arch. Pharmacol. (1990) 341 (suppl):R88.

101. GADIE B, LANE AC, MCCARTHY PS, TULLOCH IF, WALTER DS: 2- Alkyl analogues of RX 781094: a potent selective antagonist at central α₂-

adrenoceptors. Brit. J. Pharmacol. (1983) 78:312P.

102. SCHOEFFTER P, HOYER D: 5-Hydroxytryptamine 5-HT₁B and 5-HT₁D receptors mediating inhibition of adenylate cyclase activity. Pharmacological comparison with special reference to the effects of yohimbine, rauwolscine and some β-adrenoceptor antagonists. Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:285292.

103. NELSON DR, THOMAS DR: (3-H)-BRL 43694 (Granisetron), a specific ligand for 5-HT₃ binding sites in rat brain cortical membrane. Biochem. Pharmacol. (1989) 10:1693-1695.

104. COSTALL B, DOMENEY AM, GERRARD PA, KELLY MA, NAYLOR RJ: Zacopride: Anxiolytic profile in rodent and primate models of anxiety. J. Pharm. Pharmacol. (1988)40:302-305.

105. PIPER D, UPTON N, THOMAS DL, NICHOLASS J: The effects of 5-HT₃ receptor antagonists BRL 43694 and GR 38032F in animal models of anxiety. Brit. J. Pharmacol. (1988) 94:314P.

106. GARDNER CR: Recent developments in 5-HT-related pharmacology of animal models of anxiety. Pharmacol. Biochem. Behav. (1986) 24:1479-1485.

107. COLPAERT FC, MEERT TF, NIEMEGEERS CJE, JANSSEN PAJ: Behavioural and 5-HT antagonist effects of ritanserin: a pure and selective antagonist of LSD discrimination in the rat. Psychopharmacology (1985) 86:45-54.

108. DEACON R, GARDNER CF: Benzodiazepine and 5-HT ligands in a rat conflict test. Brit. J. Pharmacol. (1986) 88:330P.

109. BROCCO MJ, KOEK W, DEGRYSE A-D, COLPAERT FC: Comparative studies on the anti-punishment effects of chlordiazepoxide, buspirone and ritanserin in the pigeon, Geller-Seifter and Vogel conflict procedures. . Behav. Pharmacol. (1990) 1:403-418.

110. NIESINK RJM, VAN REE JM: Antidepressant drugs normalise the increased social behaviour of pairs and male rats induced by short term isolation. Neuropharmacology (1982) 21:1343-1348.

111. MASON P, SKINNER J, LUTTINGER D: Two tests in rats for anti- anxiety effect of clinically anxiety attenuating antidepressants. Psychopharmacology (1987) 92:30-33.

112. SEPINWALL J, COOK L: Mechanism of action of the benzodiazepines: behavioural aspect. Fed. Proc. (1980) 39:3024- 3031.

113. BECKER HC: Comparison of the effects of the benzodiazepine midazolam and three serotonin antagonists on a consumatry conflict paradigm. Pharmacol. Biochem. Behav. (1986) 24:1057- 1064.

114. KOEK W, JACKSON A, COLPAERT FC: Behavioural pharmacology of antagonists at 5-HT₂/5-HT₁c receptors. Neurosci. Biobehav. Rev. (1993) 16:95-

105.

115. FILE SE: **Metabolism disorders of the central nervous system.** Clifford Rose, (ed). Pitmans, London, pp 420-445.

116. WINTER JD: **Comparison of chlordiazepoxide, methysergide and cinanserin as modifiers of punished behaviour and as antagonists of N,N-dimethyltryptamine.** Arcb. Int. Pharmacodyn. Tber. (1972) **197**:147-159.

117. GRAEFF FG: **Tryptamine antagonists and punished behaviour.** J. Pharmacol. Exp. Therap. (1974) **189**:344-350.

118. COOK K, SEPINWALL J: **Mechanisms of action of benzodiazepines.** (1975). Costa E, Greengard P, (Eds). Raven Press, New York, pp 1-28.

119. STEIN L, WISE CD, BELLUZZI JD: **Mechanisms of action of the benzodiazepines.** (1975) Costa E, Greengard P, (Eds), Raven Press, New York, pp 29-44.

120. LEONE CML, DE AGUIR JC, GRAEFF FG: **Role of 5-hydroxytryptamine in amphetamine effects on punished and unpunished behaviour.** Psychopharmacology (1983) **80**:78-82.

121. NASHOLD BS, WILSON WP, SLAUGHTER DG: **Sensations evoked by stimulation of the midbrain of man.** J. Neurosurg. (1969) **30**:14-24.

122. OLDS ME, OLDS J: **Approach-avoidance analysis of rat diencephalon.** J. Comp. Neurol. (1963) **120**:359-295.

123. JENCK F, BROEKKAMP CLE, VAN DELFT ML: **5-HT$_{1C}$ receptors in the serotonergic control of periaqueductal gray induced aversion in rats.** Psychopharmacology (1990) **100**;372-376.

124. BECKETT SRG, MARSHALL PW, MARSDEN CA: **Intra-Periaqueductal Grey administration of mCPP potentiates a chemically-induced defence response.** Brit. J. Pharmacol. (1992) **107** (suppl 1):8P.
• Identification of the periaqueductal grey as a second site which may mediate mCPP-induced anxiety.

125. MURPHY JE: **Mianserin in the treatment of depressive illness and anxiety states in general practice.** Brit. J. Pharmacol. (1978) **5**:81S-85S.

126. RUSSEL GFM, NIAZ U, WAKELING A, SLADE PD: **Comparative double-blind trial of mianserin hydrochloride (Organon GB94) and diazepam in patients with depressive illness.** Brit. J. Clin. Pharmacol. (1978) **5**:57S-65S.

127. CONTI L, PINDER RM: **A controlled comparative trial of mianserin and diazepam in the treatment of anxiety states in psychiatric outpatients.** Int. J. Med. Res. (1979) **7**:285-289.

128. KHAN MC, BENNIE EH, STULEMEIJER SM, RAVENS MA: **Mianserin and dioxepin in the treatment of outpatient depression with anxiety.** Brit. J. Clin. Pharmacol. (1983) **15**:213S-218S.

129. CEULEMANS DLS, HOPENBROUWERS MLJA, GELDERS YG, REYNTJENS AJM: **The influence of ritanserin, a serotonergic antagonist, in anxiety disorders: a double-blind placebo-controlled study versus lorazepam.** Pharmacopsychiatry (1985) **18**:303-305.
•• Clinical evidence of the antianxiety properties of a 5-HT$_{1C/2}$ receptor antagonist.

130. BRESSA GM, MARINI S, GREGORI S: **Serotonin S2 receptor blockade and generalised anxiety disorder. A double blind study on ritanserin and lorazepam.** In. J. Clin. Pharm. Res. (1987) **VII**:111-119.

131. PANGALILA-RATU LANGI EA, JANSSEN AI: **Ritanserin the treatment of generalised anxiety disorders: a placebo-controlled trial.** Human Psychopharmacology (1988) **3**:207-212.

132. GRAEFF FG, ZUARDE AW, GIGLIO JS, LIMA FILHO EC, KARNIOL IG: **Effect of metergoline on human anxiety.** Psychopharmacology (1985) **86**:334-338.

133. KAHN RS, ASNIS GM, WETZLER S, VAN PRAAG HM: **Neuroendocrine evidence for serotonin receptor supersensitivity in patients with panic disorder.** Psychopharmacology (1988) **96**:360-364.

134. KAHN RS, WETZLER S, VAN PRAAG HM, ASNIS GM: **Behavioural indications of serotonin receptor hypersensitivity in patients with panic disorder.** Psychiatr. Res. (1988) **25**:101-104.

135. KLEIN E, ZOHAR J, GERACI MF, MURPHY DL, UHDE TW: **Anxiogenic effects of mCPP in patients with panic disorder: comparison to caffeine's anxiogenic effects.** Biol. Psychiat. (1991) **30**:973-984.

136. KAHN RS, WETZLER S, ASNIS GM, KLING MA, SUCKOW RF, VAN PRAAG HM: **Pituitary hormone responses to m-chlorophenylpiperazine in patients with panic disorder and healthy subjects.** Psychiat. Res. (1991) **37**:25-34.

137. CHARNEY DS, HENINGER GR, JATLOW PI: **Increased anxiogenic effects of caffeine in panic disorders.** Arch. Gen. Psychiat. (1985) **42**:233-243.

138. UHDE TW: **Neurobiological aspects of panic disorder.** Ballenger JC (Ed). Alan Liss, New York, pp 219-242.

139. CHARNEY DS, HENINGER GR, BREIER A: **Noradrenergic function in panic disorder: Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder.** Arch. Gen. Psychiat. (1984) **41**:751-763.

140. LIEBOWITZ MR, FYER AG, GORMAN JM: **Lactate provocation of panic attacks. I. Clinical and behavioural findings.** Arch. Gen. Psychiat. (1984) **41**:764-770.

141. WESTENBERG HGM, DEN BOER JA: **Serotonin-influencing drugs in the treatment of panic disorder.** Psychopathology (1989) **22** (suppl):68-77.
•• Failure of a 5-HT$_{1C/2}$ receptor antagonist to ameliorate panic disorder.

142. GRIEZ E, POLS H, LOUSBERG H: Serotonin antagonism in panic disorder: an open trial with ritanserin. Acta. Psychiat. Belg. (1988) 88:372-377.

143. INSEL TR, MURPHY DL, COHEN RM, ALTERMAN I, KILTS C, LINNOILA M: Obsessive-compulsive disorder: a double-blind trial of clomipramine and clorgyline. Arcb. Gen. Psychiat. (1983) 40:605-612.

144. THOREN P, ASBERG M, CRONHOLM B, JORNSTEDT L,
• TRASKMAN L: Clomipramine treatment of obsessive compulsive disorder. I. A controlled clinical trial. Arc. Gen. Psychiat. (1980) 37:1281-1285.
Identification of the clinical efficacy of 5-HT reuptake inhibitors in OCD.

145. MURPHY DL, PIGGOTT TA: A competitive examination of a role for serotonin in obsessive compulsive disorder, panic disorder and anxiety. J. Clin. Psychiat. (199) 5 (5, suppl):53-58.

146. ZAK JP, MILLER JA, SHEEHAN DV, BALSAM SLF: The potential role of serotonin uptake inhibitors in the treatment of obsessive compulsive disorder. J. Clin. Psychiat. (1988) 49 (8, suppl):23-29.

147. YARYURA-TOBIAS JS, BHAGAVAN HN: L-tryptophan in obsessive- compulsive disorders. Am. J. Psychiat. (1977) 234:1298-1299.

148. THOREN P, ASBERG M, BERTILSSON L, MELLSTROM B, SJOQVIST F, TRASKMAN L: Clomipramine treatment of obsessive compulsive disorder. II. Biochemical aspects. Arcb. Gen. Psychiat. (1980) 37:1289-1294.

149. INSEL TR: New pharmacological approaches to obsessive compulsive disorder. J. Clin. Psychiat. 51 (10, suppl) (1990):47- 51.

150. CHOUINARD G, GOODMAN W, GREIST J, JENIKE M, RASMUSSEN S, WHITE K, HACKETT E, GAFFNEY M, BICK PA: Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive-disorder. Psychopharmacology Bull. (1990) 26:279-284.

151. HOLLANDER E, DeCARIA CM, SCHNEIER FR, SCHNEIER HA, LIEBOWITZ MR, KLEIN DF: Fenfluramine augmentation of serotonin reuptake blockade antiobsessional treatment. J. Clin. Psychiat. (1990) 51:119-123.

152. ZOHAR J, MUELLER EA, INSEL TR, ZOHAR-KADOUCH
•• RC, MURPHY DL: Serotonergic responsivity in obsessive compulsive disorder: Comparison of patients and healthy controls. Arcb. Gen. Psychiat. (1987) 44:946-951.
MCPP causes OCD symptoms in OCD patients.

153. HOLLANDER E, FAY M, COHEN B, CAMPEAS R, GORMAN JM, LIEBOWITZ MR: Serotonergic and noradrenergic sensitivity in obsessive-compulsive disorder: Behavioural findings. Am. J. Psychiat. (1988) 145:1015-1018.

154. HOLLANDER E, DeCARIA CM, NITESCU A, GULLY R, SUCKOW RF, COOPER TB, GORMAN JM, KLEIN DF, LIEBOWITZ MR: Serotonin function in obsessive-compulsive disorder. Behavioural and neuroendocrine responses to oral m-chlorophenylpiperazine and fenfluramine in patients and healthy volunteers. Arcb. Gen. Psychiat. (1992) 49:2128.

155. CHARNEY DS, GOODMAN WK, PRICE LH, WOODS SW, RASMUSSEN SA, HENINGER GR: Serotonin function in obsessive-compulsive disorder: A comparison of the effects of tryptophan and m-chlorophenylpiperazine in patients and healthy subjects. Arcb. Gen. Psychiat. (1988) 45:177-185.

156. BASTANI B, NASH JF, METZER HY: Prolactin and
• cortisol responses to MK-212, a serotonin agonist, in obsessive-compulsive disorder. Arcb. Gen. Psychiat. (1990) 47:833-839.
Failure of MK-212, a 5-HT$_{1C}$ receptor agonist, to elicit OCD symptoms in OCD patients.

157. HOLLANDER E, DeCARIA C, GULLY R, NITESCU A, SUCKOW RF, GORMAN JM, KLEIN DF, LIEBOWITZ MR: Effects of chronic fluoxetine treatment on behaviour and neuroendocrine responses to meta- chlorophenylpiperazine in obsessive-compulsive disorder. Psychiat. Res. (1990) 36:1-17.

158. ZOHAR J, INSEL TR, ZOHAR-KADOUCH RC, HILL JL,
• MURPHY DLL: Serotonergic responsivity in obsessive-compulsive disorder: Effects of chronic clomipramine treatment. Arcb. Gen. Psychiat. (1988) 45:167-172.
Desensitiztion of responses to the 5-HT$_{1C}$ receptor agonist mCPP in OCD patients after chronic treatment with the clinically efficious 5-HT reuptake inhibitor, chlorimipramine.

159. GLENNON RA, ISMAIEL AE-KM, McCARTHY BG, PEROUTKA SJ: binding of arylpiperazines to 5-HT$_3$ serotonin receptors: results of a structure affinity study. Eur. J. Pharmacol. (1989) 168:387-392.

160. CUNNINGHAM KA, CALLAHAN PM, APPEL JB: Discriminative stimulus properties of the serotonin agonist MK 212. Psychopharmacology (1986) 90:193-197.

161. McBRIDE PA, DeMEO MD, SWEENEY JA, HALPER J, MANN JJ, SHEAR MK: Neuroendocrine and behavioural responses to challenge with the indirect serotonin agonist dl-fenfluramine in adults with obsessive-compulsive disorder. Biol. Psychiat. (1992) 31:19-34.

162. CRONIN SM, BILL DJ, FLETCHER A: Evidence for the
• involvement of 5-HT$_{1C}$ receptors in the anxiogenic-like effects of fenfluramine in a modified Vogel conflict test. Brit. J. Pharmacol. (1992) (in press).
Further evidence of the anxiogenic effects of 5-HT$_{1C}$ receptor activation.

163. MENINI T, BIZZI A, CACCIA S, CODEGONI A, FRACASSO C, RITTOLI E, GUISO G, PADURA IM, TADDEI C, USLENGHI A, GARATTII S: Comparative studies on

the anorectic activity of d-fenfluramine in mice, rats, and guinea pigs. *Naunyn Schmiedebergs Arcb. Pharmacol.* (1991) 343:483-490.

164. RASMUSSEN SA, GOODMAN WK, WOODS SW, HENINGER GK, CHARNEY DS: Effects of yohimbine in obsessive-compulsive disorder. *Psychopharmacology* (1987) 93:308-313.

165. GORMAN JM, LIEBOWITZ MR, FYER AJ, DILLON D, DAVIES SO, STEIN J, KLEIN DF: Lactate infusions in obsessive-compulsive disorder. *Am. J. Psychiat.* (1985) 142:864-866.

166. ZOHAR J, KLEIN EM, MUELLER EA, INSEL TR, UHDE TW, MURPHY DL: 5HT, obsessive-compulsive disorders and anxiety. *Am. Psychiat. Assoc.* Chicago (1987)111.

167. BENKELFAT C, MURPHY DL, ZOHAR J, HILL JL, GROVER G, INSEL TR: Clomipramine in obsessive-compulsive disorder. Further evidence for a serotonergic mechanism of action. *Arcb. Gen. Psychiat.* (1989) 46:23-26.

168. SCHOEFFTER I, WAEBER C, PALACIOS JM, HOYER D: The 5- hydroxytryptamine 5-HT$_{1D}$ receptor subtype is negatively coupled to adenylate cyclase in calf substantia nigra. *Naunyn Schmiedebergs Arcb. Pharmacol.* (1988) 337:602-608.

169. ZOHAR J, KINDLER S: Serotonergic probes in obsessive compulsive disorder. *Int. Clin. Psychopharmacol.* (1992) Suppl. 1:39-40.

170. ROBINS LN, HELZER JE, WEISSMAN MM, ORVASCHEL H, GRUENBERG E, BURKE JD, REGIER DA: Lifetime prevalence of specific psychiatric disorders in three sites. *Arcb. Gen. Psychiat.* (1984) 41:949-958.

171. BALLENGER JC, GOODWIN FK, MAJOR LF, BROWN GL: Alcohol and central serotonin metabolism in man. *Arcb. Gen. Psychiat.* (1979) 36:224-227.

172. ROY A, VIRKUNNEN M, LINNOILA M: Reduced central serotonin turnover in a subgroup of alcoholics. *Prog. Neuropsychopharmacol. Biol. Psychiat.* (1987) 11:173-177.

173. TAKAHASHI S, YAMANE H, KONDO H, TANI N, KATO N: CSF monoamine metabolites in alcoholism, a comparative study with depression. *Folia Psychiatrica et Neurologia Japanica* (1974) 28:237-354.

174. BANKI CM: 5-Hydroxytryptamine content of the whole blood in psychiatric illness and alcoholism. *Acta. Psychiat. Scand.* (1978) 57:232.

175. BANKI CM: Factors influencing monoamine metabolites and tryptophan in patients with alcohol dependence. *J. Neural Transm.* (1981) 50:98-101.

176. MCBRIDE WJ, MURPHY JM, LUMENG L, LI TK: Serotonin, dopamine and GABA involvement in alcohol drinking of selectively bred rats. *Alcobol* (1990) 7:199-205.

177. HOLMAN RB, SNAPE BM: Effects of ethanol on 5-hydroxytryptamine release from corpus

striatum in vivo. *Alcobol* (1985) 2:249-253.

178. TYTELL M, MYERS RD: Metabolism of [^{14}C]-serotonin in the caudate nucleus, hypothalamus and reticular formation of the rat after ethanol administration. *Biochem. Pharmacol.* (1973) 2:361- 372.

179. MURPHY JM, McBRIDE WJ, GATTO GJ, LUMENG L, LI TK: Effects of acute ethanol administration of monoamine and metabolite content in forebrain regions of ethanol-tolerant and nontolerant alcohol preferring (P) rats. *Pharmacol. Biochem. Bebav.* (1988) 29:169- 174.

180. MORINAN A: Reduction in striatal 5-hydroxytryptamine turnover following chronic administration of ethanol to rats. *Alcobol* (1987) 22:53-60.

181. ZABIK JK, BINKENDO K, ROACHE JD: Research advances in new psychopharmacologic treatment for alcoholism. Naranjo CA, Sellers EM, (Eds). Elsevier, Amsterdam, (1985), pp 75-93.

182. GORELICK DA: Effects of fluoxetine on alcohol consumption. *Alcobol* (1986) 10:113.

183. MURPHY JM, McBRIDE WJ, LUMENG L, LI TK: Effects of serotonergic agents on ethanol intake of the high alcohol drinking (HAD) line of rats. *Pharmacol. Biochem. Bebav.* (1987) 26:389-392.

184. MURPHY JM, WALLER MB, GATTO GJ, McBRIDE WJ, LUMENG L, LI TOK: Effects of fluoxetine on the intragastric self- administration of EtOH in the alcohol preferring P line of rats. *Alcobol* (1988) 5:283-286.

185. GILL K, FILION Y, AMIT Z: A further examination of the effects of sertraline on voluntary ethanol consumption. *Alcobol* (1988) 5:355-358.

186. LEVY A, McBRIDE WJ, MURPHY JM: Effects of intra-accumbens infusions of DA and 5-HT on ethanol intake of alcohol-preferring (P) rats (abstract). *Alcobolism* (1989) 13:305.

187. SVENSSON L, ENGEL J, HARD E: Effects in the 5-HT receptor agonist 8-OH-DPAT on EtOH preference in the rat. *Alcobol* (1989) 6:17-21.

188. PRIVETTE TH, HORNSBY RL, MYERS RD: Buspirone alters alcohol drinking induced in rats by tetrahydropapaveroline injected into brain monoaminergic pathways. *Alcobol* (1987) 5:147-152.

189. WALTERS JK: Effects of PCPA on the consumption of alcohol, water and other solutions. *Pharmacol. Biochem. Bebav.* (1977) 6:377383.

190. PARKER LF, RADOW BL: Effects of parachlorophenylalanine on ethanol self-selection in the rat. *Pharmacol. Biochem. Bebav.* (1976) 4:535-540.

191. ROCKMAN GE, BROWN ZW, BOURQUE C, OGREN S-O: An investigation of the mechanism of action of 5-hydroxytryptamine in the suppression of ethanol intake. *Neuropharmacology* (1982) 21:341- 347.

192. WEISS F, MITCHENER M, BLOOM FE, KOOB GF: Free-choice responding for ethanol versus water in alcohol preferring (P) and unselected Wistar rats is differentially modified by naloxone, bromocriptine and methysergide. *Psychopharmacology* (1990) 101:178-186.

193. HO AKS: Experimental studies on alcoholism I. Increase in alcohol preference by 5,6,dihydroxytryptamine and brain acetylcholine. *Psychopharmacology* (1974) 40:101-107.

194. KHANMAA K: Alcohol intake in the rat after lowering brain 5-hydroxytryptamine content by electrolytic midbrain raphe lesions, 5,6-dihydroxytryptamine or p-chlorophenylalanine. *Med. Biol.* (1976) 54:203-209.

195. NARANJO CA, SELLERS EM: Recent developments in alcoholism. (Vol &). Galanter M (Ed), Plenum, (1989) pp 255-266.

196. NARANJO CA, POULOS CX, BREMNER KE, LANETOT KL: Citalopram decreases desireability, liking, and consumption of alcohol in alcohol-dependent drinkers. *Clin. Pharmacol. Ther.* (1992) 51:729-939.

197. GERRA G, CACCAVARI R, DELSIGNORE R, BOCCHI R, FERTONANI G, PASSERI M: Effects of fluoxetine and CA-acetyl homotaurinate on alcohol intake in familial and non-familial alcoholic patients. *Curr. Therap. Res.* (1992) 52:291-295.

198. BRUNO F: Buspirone in the treatment of alcoholic patients. *Psychopharmacology* (1989) 22 (suppl):49-59.

199. OLIVERA AA, SARVIS S, HEARD C: Anxiety disorders coexisting with substance dependence: treatment with buspirone. *Curr. Therap. Res.* (1990) 47:52-60.

200. TOLLEFSON GD, MONTAGUE-CLOUSE J, LANCASTER SP: Buspirone in comorbid alcohol dependency and generalized anxiety disorders. *Drug Therapy* (1990) 20 (Suppl):35-50.

201. DEMONTIGNY C, BLIER P, CHAPUT Y: Electrophysiologically identified serotonin receptors in the cat CNS-effect of antidepressant treatment. *Neuropharmacology* (1984) 23:1511-1519.

202. BENKELFAT C, MURPHY DL, HILL JL, GEORGE DT,
•• NUTT D, LINNOILA M: Ethanol like properties of the serotonergic partial agonist m-chlorophenylpiperazine in chronic alcoholic patients. *Arch. Gen. Psychiat.* (1991) 48:383.
MCPP reported to induce craving in withdrawn alcoholics.

203. SELLERS EM, HIGGINS GA, SOBELL MB: 5-HT and
• alcohol abuse. *Trends in Pharmacol. Sci* (1992) 13:69-75.
Review of the role of 5-HT in the effects of alcohol.

204. SIGNS SA, SCHECHTER MD: The role of dopamine and serotonin receptors in the mediation of the ethanol interoceptive cue. *Pharmacol. Biochem. Behav.* (1988) 30:55-64.

205. KENNETT GA, DOURISH CT, CURZON G: 5-HT$_{1B}$ agonists induce anorexia at a postsynaptic site.

Eur. J. Pharmacol. (1987) 141:429-435.

206. MODELL JG, MOUNTZ JM, BEESFORD TP: Basal ganglia/limbic striatal and thalamocortical involvement in craving and loss of control in alcoholism. *J. Neuropsychiat. Clin. Neurosci.* (1990) 2:123-144.

207. KUSHNER MG, SHER KJ, BEITMAN BD: The relation between alcohol problems and the anxiety disorders. *Am. J. Psychiat.* (1990) 147:685-695.

208. GOLDBERG HL, FINNERTY RJ: The comparative efficacy of buspirone and diazepam in the treatment of anxiety. *Am. J. Psychiat.* (1979) 136:1184-1187.

209. MEERT TF, JANSSEN PAJ: Ritanserin, a new
•• therapeutic approach for drug abuse. Part 1: Effects on alcohol. *Drug Development Res.* (1991) 24:235-249.
Evidence that a 5-HT$_{1C/2}$ receptor antagonist may reduce alcohol preference in rats.

210. KENNETT GA, D'ARCY S, BLACKBURN TP: Effect of 5-HT receptor antagonists on rat ethanol preference. *J. Psychopharmacol.* (1992) Abstr. BAP/EPBS meeting. A76.

211. MONTI JM, ALTERWAIN P: Ritanserin decreases
•• alcohol intake in chronic alcoholics. *Lancet* (1991) 337:60.
A 5-HT$_{1C/2}$ receptor antagonist was reported to reduce alcohol intake in alcoholics.

212. SCHECHTER LE, SIMANSKY KT: 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI) exerts an anorexic action that is blocked by 5-HT$_2$ antagonists in rats. *Psychopharmacol.* (1988) 94:342-346.

213. LUCKI I, FRAZER A: Behavioural effects of indole and piperazine type serotonin receptor antagonists. *Am. Soc. Neurosci.* (1982) 8 (Abstr):101.

214. SADZOT B, BARABAN JM, GLENNON RA, LYON RA, LEONHEART S, JAN CR, TITELER M: Hallucinogenic drug interactions at human brain 5-HT$_2$ receptors: implications for treating LSD-induced hallucinogenesis. *Psychopharmacology* (1989) 98:495-499.

215. MEERT TF, AWOUTERS F, NIEMEGEERS CJE, SCHELLEKENS KHL, JANSSEN PAJ: Ritanserin reduces abuse of alcohol, cocaine, and fentanyl in rats. *Pharmacopsychiat.* (1991) 24:159-163.

216. MEERT TF, JANSSEN PAJ: Ritanserin, a new
• therapeutic approach for drug abuse. Part 2: Effects on cocaine. *Drug Development Res.* (1991) 25:39-53.
This data suggests that the effects of a 5-HT$_{1C}$ receptor antagonist on alcohol may also apply to cocaine preference in rats. This type of drug may therefore inhibit addiction to other drugs of abuse.

217. MEERT TF, JANSSEN PAJ: Ritanserin, a new therapeutic approach for drug abuse. Part 3: Effects on fentanyl and sucrose. *Drug Development Res.* (1991) 25:55-66.

218. IMPERATO A, DI CHIARA G: Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. *J. Pharmacol. Exp. Therap.* (1986) 239:219-228.

219. VAN PRAAG HM, KAHN RS, ASNIS GM, WETZLER S, BROWN SL, BLEICH A, KORN ML: New concepts in depression. Pierre Fabre monograph series 2. Macmillan (1988), pp 96-119.

220. CAMARA EG: Open study on the use of cyproheptadine in hypercortisolaemic, unipolar, depressed patients. *Biol. Psychiat.* (1991) 29:201A.

221. REYNTJENS A, GELDERS YG, HOPPENBROUWERS M-LJA,
    • BUSSCHE GV: Thymosthenic effects of ritanserin (R 55667), a centrally acting serotin-S2 receptor blocker. *Drug Dev. Res.* (1986) 8:205-211.
    A 5-HT$_{1C/2}$ receptor antagonist reported to have antidepressant-like properties.

222. KLIESER E, STRAUSS WH: Study to establish the indication for the selective S2-antagonist ritanserin. *Pharmacopsychiat.* (1988) 21:391-393.

223. NAPPI G, SANDRINI G, GRANELLA F, RUIZ L, CERUTTI
    • G, FRACCHINETTI F, BLANDINI F, MANZONI GC: A new 5-HT$_2$ antagonist (Ritanserin) in the treatment of chronic headache with depression. A double-blind study vs amitryptyline. *Headache* (1990) 30:439-444.
    Reported efficacy of a 5-HT$_{1C/2}$ receptor antagonist in migraine.

224. LAWLOR BA, SUNDERLAND T, MELLOW AM, HILL JL, NEWHOUSE PA, MURPHY DL: A preliminary study of the effects of intravenous m-chlorophenyl-piperazine, a serotonin agonist, in elderly subjects. *Biol. Psychiat.* (1989) 25:679-686.

225. LAWLOR BA, SUNDERLAND T, MELLOW AM, HILL JL, MOLCHAN SE, MURPHY DL: Hyperresponsivity to the serotonin agonist, m-chlorophenyl-piperazine in Alzheimer's disease. *Arch. Gen. Psychiat.* (1989) 46:542-549.

226. KAHN RS, WETZLER S, ASNIS GM, PAPOLOS D, VAN PRAAG HM: Serotonin receptor sensitivity in major depression. *Biol. Psychiat.* (1990) 28:358-362.

227. MELLOW AM, LAWLOR BA, SUNDERLAND T, MUELLER
    • EA, MOLCHAN SE, MURPHY DL: Effects of daily oral m-chlorophenylpiperazine in elderly depressed patients. Initial experience with a serotonin agonist. *Bio. Psychiat.* (1990) 28:588-594.
    Interesting antidepressant response to subchronic mCPP.

228. ANDERSON JL: Serotonin receptor changes after chronic antidepressant treatments: ligand binding, electrophysiological and behavioral studies. *Life Sci.* (1983) 32:1791-1801.

229. LUCKI I, WARD HA, FRAZER A: Effect of 1-(m-chlorophenyl)piperazine and 1-(m-trifl-uoromethylphenyl)piperazine on locomotor activity. *J. Pharmacol. Exp. Therap.* (1989) 249:155-164.

230. BERENDSEN HHG, BROEKAMP CLE: Attenuation of 5-

HT$_{1A}$ and 5-HT$_2$ but not 5-HT$_{1C}$ receptor mediated behaviour in rats following chronic treatment with 5-HT receptor agonists, antagonists or antidepressants. *Psychopharmacology* (1991) 105:219-224.

231. BERENDSEN HHG, JENCK F, BROEKAMP CLE:
    • Involvement of 5-HT$_{1C}$ receptors in drug-induced penile erections in rats. *Psychopharmacology* (1990) 101:57-61.
    5-HT$_{1C}$ receptor activation reported to mediate penile erection in rats.

232. COHEN RM, AULAKH CS, MURPHY DL: Long term
    • clorgyline treatment antagonizes the eating and motor function responses to m-chlorophenylpiperazine. *Eur. J. Pharmacol* (1983) 94:175-179.
    First data suggesting that antidepressants may desensitize 5-HT$_{1C}$ receptors.

233. WOZNIAK KM, AULAKH CS, HILL JL, MURPHY DL:
    • Hyperthermia induced by m-CPP in the rat and its modification by antidepressant treatments. *Psychopharmacology* (1989) 97:269-274.
    Evidence that mCPP-induced hyperthermia in rats may be 5-HT$_{1C}$ receptor mediated.

234. MAJ J, MORYL E: Effects of sertraline and citalopram given repeatedly on the responsiveness of 5-HT receptor populations. *J. Neural. Transm.* (1992) 88:143-156.

235. AULAKH CS, COHEN RM, HILL JL, MURPHY DL, ZOHAR J: Long-term imipramine treatment enhances the locomotor and food intake suppressant effects of m-CPP in rats. *Brit. J. Pharmacol.* (1987) 91:747-752.

236. AULAKH CS, HAASS M, ZOHAR J, WOZNIAK KM, HILL JM, MURPHY DL: Long term imipramine treatment potentiates m-chlorophenyl-piperazine-induced changes in prolactin but not corticosterone or growth hormone levels in rats. *Pharmacol. Biochem. Behav.* (1989) 32:37-42.

237. SILLS MA, LUCKI I, FRAZER A: Development of selective serotonin behavioural syndrome and suppression of either 5-MEODMT or mCPP. *Life Sci.* (1985) 36:2463-2469.

238. FREO U, HOLLOWAY HW, GRIEG NH, SONCRANT TT: Chronic treatment with meta-chlorophenylpiperazine (m-CPP) alters behavioral and cerebral metabolic responses to the serotonin agonists mCPP and quipazine but not 8-hydroxy-2(di-N-propylamino)tetralin. *Psychopharmacology* (1992) 107:30-38.

239. ULRICHSEN J, PARTILLA JS, DAX EM: Long term administration of m-chlorophenylpiperazine (mCPP) to rats induces changes in serotonin receptor binding, dopamine levels and locomotor activity without altering prolactin and corticosterone secretion. *Psychopharmacology* (1992) 107:229-235.

240. WONG DT, THRELKELD PG, ROBERTSON DW: Affinities of fluoxetine, its enantiomers and other inhibitors of serotonin uptake for subtypes of serotonin receptors.

Neuropsychopharmacology (1991) 5:43-47.

241. BREWERTON TD, MURPHY DL, MUELLER EA, JIMERSON
•• DC: Induction of migraine-like headaches by
the serotonin agonist m-chlorophenyl-
piperazine. *Clin. Pharmacol. Ther.* (1988) 43:605-
609.

MCPP reported to induce migraine-like headaches
particularly in migraineurs.

242. GORDON ML, LIPTON RB, BROWN SL: A
neuroendocrine challenge study with mCPP in
migraine subjects and normal controls.
Cephalalgia (1992) (in press).

243. FOZARD JR, GRAY JA: 5-HT$_{1C}$ receptor activation:
•• a key step in the initiation of migraine? *Trends
in Pharmacol. Sci.* (1989) 10:307-309.

Hypothesis of 5-HT$_{1C}$ receptor activation causing and
preventing migraine proposed

244. WINTHER K: Ketanserin, a selective serotonin
antagonist, in relation to platelet aggregation
and migraine attack rate. *Cephalalgia* (1985) 5
(suppl 3):402-403.

245. BOWMAN WC, RAND MJ: **Textbook of
pharmacology**. Blackwell Scientific Publications,
Oxford (1980).

246. DOENICKE A, BRAND J, PERRIN V: Possible benefit
of GR 43175, a novel 5-HT$_1$-like receptor
agonist, for the acute treatment of severe
migraine. *Lancet* (1988) 1:1309-1311.

247. HUMPHREY PPA: 5-Hydroxytryptamine and the
pathophysiology of migraine. *J. Neurol.* (1991)
238:S38-S44.

248. FOZARD JR: 5-HT in migraine. In Sandler M,
Collins GM (eds). Migraine: a spectrum of ideas.
Oxford University Press, Oxford (1990) pp 128-146.

249. DAVIES PTG, STEINER TJ: Serotonin S2 receptors
• and migraine: a study with the selective
antagonist ICI 169,369. *Headache* (1990) 30:340-
343.

Modest antimigraine effect of a 5-HT$_{1C/2}$ receptor
antagonist in a clinical trial.

250. BLACKBURN TP, THORNBER CW, PEARCE RJ, COX B: In
vitro studies with ICI 169,369, a chemically
novel 5-HT antagonist. *Eur. J. Pharmacol.* (1988)
150:247-256.

251. COUCH JR, HASSENEIN RS: **Amytryptaline in
migraine prophylaxis**. *Arch. Neurol.* (1979)
36:695-699.

252. MARKELY HG, GASSER PA, MARKLEY ME, PRATT SM:
Fluoxetine in prophylaxis of headache:
Clinical experience. *Cephalagia.* (1991) 11:S11.

253. ADLEY C, STRAUMANIS J, CHESSON A: Fluoxetine
prophylaxis of migraine. *Headache* (1992)
32:101-104.

254. GRIFFITHS WJ, LESTER BK, COULTER JD, WILLIAMS HL:
Tryptophan and sleep in young adults.
Psychophysiology (1972) 9:245-356.

255. HARTMANN E, CRAVENS J. LIST S: Hypnotic effects
of 1-tryptophan. *Arch. Gen. Psychiatry* (1974)
31:394-397.

256. MENDELSON WB, GILLIN JC, WYATT RJ: **Human
sleep and its disorders**. Plenum, New York,
(1977) pp 21-62.

257. JOUVET M: The role of monoamines and acetyl-
containing neurons in the regulation of the
sleep-waking cycle. *Erg. Physiol. Biol. Chem. Exp.
Pharmakol.* (1972) 64:166-307.

258. WYATT RJ: The serotonin-catecholamine dream
bicycle: a clinical study. *Biol. Psychol.* (1972)
5:33-63.

259. KAFI-DE ST HILAIRE S, HJORTH S, GAILLARD JM: **Brain
5-HT$_{1A}$ receptors: Behavioural and
neurochemical pharmacology**. Dourish CT,
Ahlenius S, Hutson PH, (Eds): Ellis Horwood Ltd,
Chichester, U.K. (1987):135-139.

260. DZOLJIC MR, SAXENA PR, UKPONMWAN OE:
Activation of "5-HT$_1$- like" receptors stimulates
wakefulness. *Brit. J. Pharmacol.* (1986) 89:522P.

261. SEIDEL WF, COHEN SA, BLIWISE NG, DEMENT WC:
Buspirone, an anxiolytic without sedative
properties. *Psychopharmacology* (1985) 87:371-
373.

262. LAWLOR BA, NEWHOUSE PA, BALKIN TJ, MOLCHAN SE,
• MELLOW AM, MURPHY DL, SUNDERLAND T: A
preliminary study of the effects of nighttime
administration of the serotonin agonist,
m-CPP, on sleep architecture and behaviour in
healthy volunteers. *Biol. Psychiat.* (1991) 29:281-
286.

First study revealing sleep disruption after mCPP.

263. SHARPLEY AL, KATSUDA Y, WARE CJG, WALSH AES,
COWEN PJ: The effect of mCPP on sleep in
healthy volunteers. *J. Psychopharmacol* (1992)
Abstr BAP/EPBS meeting, A7.

264. NICHOLSON AN, PASCO PA: 5-Hydroxytryptamine
and noradrenergic uptake inhibition: Studies
on sleep in man. *Neuropharmacology* (1986)
256:1079-1083.

265. DUGOVIC C, WAUQUIER A: 5-HT$_2$ receptors could
• be primarily involved in the regulation of
slow-wave sleep in the rat. *Eur. J. Pharmacol.*
(1987) 137:145-146.

A 5-HT$_{1C/2}$ receptor antagonist was observed to increase
slow wave, but decrease rapid eye movement in this rat
sudy.

266. BJORVATN B, URSIN R: Effects of Zimeldine, a
selective 5-HT reuptake inhibitor, combined
with ritanserin, a selective 5-HT$_2$ antagonist, on
waking and sleep stages in rats. *Behav. Brain
Res.* (1990) 40:239-246.

267. PASTEL RH, FERNSTROM JD: Short-term effects of
fluoxetine and trifluoromethylphenyl-
piperazine on electroencephalographic sleep
in the rat. *Brain Res.* (1987) 436:92-102.

268. KAFI-DE ST HILAIRE S, MERCIA H, GAILLARD JM: The
effects of indalpine - a selective inhibitor of
5-HT uptake - on rat paradoxical sleep. *Eur. J.
Pharmacol.* (1984) 98:413-418.

269. SOMMERFELT L, HAUGE ER, URSIN R: Similar effects
on REM sleep but differential effect on slow

wave sleep of the 5-HT uptake inhibitors zimeldine and alaproclate in cats and rats. *J. Neural Trans.* (1987) 68:127-144.

270. HILAKIVI I, KOVALA T, LEPPAVUORI A, SHVALOFF A: Effects of serotonin and noradrenaline uptake blockers on wakefulness and sleep in cats. *Pharmacol. Toxicol.* (1987) 60:161-166.

271. CLARENBACH P, BIRMANNS B, KRATZSCHMAR S, JAURSCH-HANCKE C: Sleep pattern and nocturnal plasma profiles of HGH, prolactin and cortisol in man after the serotonin-antagonist ritanserin and the GABA-agonist gabapentin. *Sleep Res.* (1986) 15:29.

272. IDZIKOWSKI C, MILLS FJ, GLENNARD R: 5-
• Hydroxytryptamine-2-antagonist increases human slow wave sleep. *Brain Res.* (1986, 378:164-168.
Slow wave sleep enhancing and rapid eye movement sleep inhibiting effects of a 5-HT$_{1C/2}$ receptor antagonist observed in this clinical study.

273. IDZIKOWSKI C, COWN PJ, NUTT D, MILLS FJ: The effects of chronic ritanserin treatment on sleep and the neuroendocrine response to l-tryptophan. *Psychopharmacology* (1987) 93:416-420.

274. DECLERCK AC, WAUQUIER A, VAN DER HAM-VELTMAN PHM, GELDERS Y: Increase in slow-wave sleep in humans with the serotonin-S2 antagonist ritanserin. *Curr. Therap. Res.* (1987) 41:427-432.

275. ADAM K, OSWALD I: Effects of repeated ritanserin on middle- aged poor sleepers. *Psychopharmacology* (1989) 99:219-221.

276. IDZIKOWSKI C, MILLS FJ, JAMES RJ: A dose-response study examining the effects of ritanserin on human slow wave sleep. *Brit. J. Clin. Pharmacol.* (1991) 31:193-196.

277. PAIVA T, WAUQUIER A, LARA E, LARGO R, LEITANO JN: Effects of ritanserin on sleep disturbances of dysthymic patients. *Psychopharmacology* (1988) 96:395-399.

278. RUIZ-PRIMO E, HARO R, VALENCIA M: Polysomnographic effects of ritanserin in insomniacs in a crossed double-blind controlled study. *Sleep Res.* (1989) 18:72.

279. DAHLITZ M, WELLS P, JAMES R, IDZIKOWSKI C, PARKES JD: Treatment of insomnia with ritanserin. *Lancet* (1990) 336:379.

280. TORMEY WP, BUCKLEY MP, O'KELLY DA, CONBOY J, PINDER RM, DARRAGH MD: Sleep-endocrine profile of the antidepressant mianserin. *Curr. Med. Res. Opinion* (1980) 6:456-460.

281. GENCO S, PUCA FM, SPECCHIO LM, INTERNO S, CASTRIOTTA R, LEOMANNI R, DAMMACCO F: Metergolina e sonno notturno nell, uomo normale. *Boll. Soc. Ital. Biol. Sper.* (1977) 53:1403-1406.

282. SOLOMON RA, SHARPLEY AL, COWEN PJ: Increased slow-wave sleep with 5-HT$_2$ receptor antagonists: Detection by ambulatory ECG recording and automatic sleep stage analysis. *J.*

Pharmacol. (1989) 3:125-129.

283. SPIEGEL R: Sleep 1980. 5th European congress on sleep research. Koella WP, (Ed): Karger, Basel, (1981), pp 275-278.

284. MENDELSON WB, JACOBS LS, REICHMAN JD, OTHMER E, CRYER PE, TRIVEDI B, DAUGHADAY WH: Methysergide: suppression of sleep related prolactin excretion and enhancement of sleep related growth hormone secretion. *J. Clin. Invest.* (1975) 56:690-697.

285. DUGOVIC C, WAUQUIER A, LEYSEN JE, MARRANNES R, JANSSEN PAJ: Functional role of 5-HT$_2$ receptors in the regulation of sleep and wakefulness in the rat. *Psychopharmacology* (1989) 97:436-442.

286. TORTELLA FC, ECHEVARRIA E, PASTEL RH, COX B, BLACKBURN TP: Suppressant effects of selective 5-HT$_2$ antagonists on rapid eye movement sleep in rats. *Brain Res.* (1989) 485:294-300.

287. DAVENNE D, DUGOVIC C, FRANC B, ADRIEN J: Slow wave sleep: Physiological, pathophysiological and functional aspects. Raven Press, New York, (1989), pp 21-30.

288. NEIL JC, COOPER SJ: Evidence that d-fenfluramine anorexia is mediated by 5-HT$_1$ receptors. *Psychopharmacology* (1989) 97:213- 218.

289. HUTSON PH, DONOHOE TP, CURZON G: Infusion of
• the 5- hydroxytryptamine agonists RU 24969 and TFMPP into the paraventricular nucleus of the hypothalamus causes hypophagia. *Psychopharmacology* (1988) 95:550-552.
Evidence that 5-HT$_{1C}$-mediated hypophagia in rats may be mediated by the paraventricular nucleus of the hypothalmus.

290. KENNETT GA, CURZON G: The antiemetic trimethobenzamide prevents hypophagia due to acetyl salicylate, but not to 5-HT$_{1B}$ or 5-HT$_{1C}$ agonists. *Psychopharmacology* (1988) 96:101-103.

291. CLINESCHMIDT BV, MCGUFFIN JC, PFEUGER AB, TOTARO JA: A 5- hydroxytryptamine-like mode of anorectic action for 6-chloro-2-(1-piperazinyl)-pyrazine (MK 212). *Brit. J. Pharmacol.* (1978) 62:579-589.

292. SCHECHTER LE, SIMANSKY KT: 1-(2,5-dimethoxy-4-iodophenyl)-2- aminopropane (DOI) exerts an anorexic action that is blocked by 5-HT$_2$ antagonists in rats. *Psychopharmacology* (1988) 94:342-346.

293. HEWSON G, LEIGHTON GE, HILL RG, HUGHES J: Quipazine induces food intake in the rat by activation of 5-HT$_2$ receptors. *Brit. J. Pharmacol.* (1989) 95:598-604.

294. WILKINSON LO, DOURISH CT: Serotonin receptor subtypes: Basic and clinical aspects. Wiley-Liss, inc., (1991), pp 147-210.

295. DOURISH CT, CLARK ML, FLETCHER A, IVERSEN SD: Evidence that blockade of postsynaptic 5-HT$_1$ receptors elicits feeding in satiated rats. *Psychopharmacology* (1989) 97:54-58.

296. FLETCHER PJ: Increased food intake in satiated rats induced by the 5-HT antagonists

methysergide, metergoline and ritanserin. *Psychopharmacology* (1988) 96:237-242.

297. MASSI M, MARINI S: Effects of the 5-HT₂ antagonist ritanserin on food intake and on 5-HT-induced anorexia in the rat. *Pharmacol. Biochem. Behav.* (1987) 26:333-340.

298. BAXTER MJ, MILLER AA, SOROKO FE: The effect of cyproheptadine on food consumption in the fasted rat. *Brit. J. Pharmacol.* (1970) 39:229-230.

299. GHOSH MN, PARVATHY S: The effect of cyproheptadine on water and food intake and on body weight in the fasted adult and weanling rats. *Brit. J. Pharmacol.* (1973) 48:328-329.

300. SWIERGIEL AH, PETERS G: Failure of serotonin antagonist pizotifen to stimulate feeding or weight gain in free-feeding rats. *Pharmacol. Biochem. Behav.* (1990) 35:61-67.

301. LAVENSTEIN AF, LASAGNA L, VAN METRE TE: Effect of
• cyproheptadine on asthmatic children, study of appetite, weight gain and linear growth. *JAMA* (1962)180:912-916.
Hyperphagic effects of a putative 5-HT₁C/₂ receptor antagonist in man reported.

302. BERGEN SS: Appetite stimulating properties of cyproheptadine. *Am. J. Dis. Child.* (1964) 108:270-273.

303. KAHN RS, WETZLER S: m-Chlorophenylpiperazine as a probe of serotonin function. *Bioll Psychiat.* (1991) 30:1139-1166.

304. ROWLAND NE, CARLTON J: Neurobiology of an anorectic drug: Fenfluramine. *Prog. in Neurobiol.* (1986) 27:13-62.

305. HEWSON G, LEIGHTON GE, HILL RG, HUGHES J: Ketanserin antagonises the anorectic effect of DL-fenfluramine in the rat. *Eur. J. Pharmacol.* (1988) 145:227-230.

306. GARATTINI S, MENNINI T, BENDOTTI C, INVERNIZZI R, SAMANIN R: Neurochemical mechanism of action of drugs which modify feeding via the serotonergic system. *Appetite* (1986) 7 (Suppl):15-38.

307. GIBSON EL, KENNEDY AJ, CURZON G: D-
• fenfluramine and D-norfenfluramine hypophagia: involvement of postsynaptic 5-HT₁C receptors? *J. Psychopharmacol.* (1992) Abstr. BAP/EPBS Meeting: A83.
Fenfluramine-induced hypophagia in rats concluded to be 5-HT₁C receptor-mediated in this study.

308. ORZACK MH, FRIEDMAN LM, MARBY DW: Weight changes on fluoxetine as a function of baseline weight in depressed outpatients. *Psychopharmacology Bull.* (1990) 26:327-330.

309. RASMUSSEN JGC, JOHNSTON AM, STEWART B, PALMER KJ: Comparative effects of the selective serotonergic uptake inhibitors paroxetine and fluoxetine on food intake in rats and effect of paroxetine on body/weight in depressed patients. *J. Psychopharmacol.* (1990) 4:300.

310. ROWLAND N, ANTELMAN SM, KOCAN D: Differences

among serotonergic anorectics in a cross-tolerance paradigm: Do they act on serotonin systems? *Eur. J. Pharmacol.* (1982) 81:57-66.

311. GOUDIE AJ, THORNTON EW, WHEELER TJ: Effect of Lilly 110140, a specific inhibitor of 5-hydroxytryptamine uptake on food intake and on 5-hydroxytryptophan-induced anorexia. Evidence for serotonergic inhibition of feeding. *J. Pharm. Pharmacol.* (1976) 28:318-320.

312. LEANDER JD: Fluoxetine suppressed palatability-induced ingestion. *Psychopharmacology* (1987) 91:285-287.

313. GILL K, AMIT ZA: Effects of serotonin uptake blockade on food water and ethanol consumption in rats. *Alcoholism: Clin. Exp. Res.* (1987) 11:444-449.

314. DUMONT C, LAURENT J, GRANDADAM A, BOISSIER JR: Anorectic properties of a new long acting serotonin uptake inhibitor. *Life Sci.* (1981) 28:1939-1945.

315. LUCKI K, KREIDER MS, SIMANSKY KJ: Reduction of feeding behaviour by the serotonin uptake inhibitor sertraline. *Psychopharmacology* (1988) 96:289-295.

316. NIELSEN JA, CHAPIN DS, JOHNSON JL, TORGERSEN LK: Sertraline, a serotonin-uptake inhibitor, reduces food intake and body weight in lean rats and genetically obese mice. *Am. J. Clin. Nutr.* (1992) 55:185S-188S.

317. WONG DT, REID LR, THRELKELD PG: Suppression of food intake by fluoxetine: comparison of enantiomers and effects of serotonin antagonists. *Pharmacol. Biochem. Behav.* (1988) 31:475-479.

318. WEISS GF, PAPADAKOS P, KNUDSON K, LEIBOWITZ SF: Medial hypothalamic serotonin: Effects on deprivation and norepinephrine-induced eating. *Pharmacol. Biochem. Behav.* (1986) 25:1223-1230.

319. FLETCHER PJ, BURTON MJ: Dissociation of the anorectic actions of 5-HTP and fenfluramine. *Psychopharmacology* (1986) 89:216-220.

320. BAKER BJ, DUGGAN JP, BARBER DJ, BOOTH DA: Effects of dl-fenfluramine and xylamidine on gastric emptying of maintenance diet in freely feeding rats. *Eur. J. Pharmacol.* (1988) 150:137-142.

321. FERGUSON JM, FEIGHNER JP: Fluoxetine-induced weight loss in overweight nondepressed humans. *Int. J. Obesity* (1987) 11 (Suppl):179S-184S.

322. LEVINE LR, ROSENBLATT S, BOSOMWORTH JC: Use of serotonin reuptake inhibitor, fluoxetine in the treatment of obesity. *Int. J. Obesity* (1987) 11 (suppl):185S-190S.

323. LEVINE LR, ENAS GG, THOMPSON WL, BYYNY RL, DAUER AD, KIRBY RW, KREINDLER TG, LEVY B, LUCAS CP, MCILWAIN HH, NELSON EB: Use of fluoxetine, a selective serotonin-uptake inhibitor in the treatment of obesity: a dose-response study. *Int.*

J. Obesity (1989) 13:635-645.

324. ROBINSON PH, CHECKLEY SA, RUSSELL GFM: Suppression of eating by fenfluramine in patients with Bulimia Nervosa. *Brit. J. Psychiat.* (1985) 146:169-176.

325. BLOUIN AG, BLOUIN JH, PEREZ EL, BUSHNIK T, ZURO C: Treatment of bulimia with fenfluramine and desipramine. *J. Clin. Psychopharmacol.* (1988) 8:261-269.

326. WALSH BT, GLADIS M, ROOSE SP, STEWART JW, STETNER F, GLASSMAN AH: Phenelzine vs placebo in 50 patients with bulimia. *Arch. Gen. Psychiat.* (1988) 45:471-475.

327. KENNEDY SH, PIRAN N, WALSH JJ, PRENDERGAST P, MAINPRIZE E, SHYNOT C, GARFINKEL PE: A trial of isocarboxazid in the treatment of bulimia nervosa. *J. Clin. Psychopharmacol.* (1988) 8:391-396.

328. FREEMAN CPL, HAMPSON M: Fluoxetine as a treatment for bulimia nervosa. *Int. J. Obesity* (1987) 11 (suppl 3):171-177.

329. POPE HG, KECK PE, McELROY SM, HUDSON JL: A placebo-controlled study of trazodone in bulimia nervosa. *J. Clin. Psychopharmacol.* (1989) 9:254-259.

330. GOLDBLOOM DS, KENNEDY SH: Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. *J. Clin. Psychiat.* (1991) 52:261-262.

331. BARLOW J, BLOUIN J, BLOUIN A, PEREZ E: Treatment of bulimia with desipramine: a double-blind crossover study. *Can. J. Psychiat.* (1988) 33:129-133.

332. HUGHES PL, WELLS LA, CUNNINGHAM CJ, ILSTRUP DM: Treating bulimia with desipramine: a placebo-controlled double-blind study. *Arch. Gen. Psychiat.* (1986) 43:182-186.

333. PRICE WA, BABAI MR: Antidepressant drug therapy for bulimia: Current status revisited. *J. Clin. Psychiat.* (1987) 48:385.

334. SABINE EJ, YONACE A, FARRINGTON AJ, BARRAT KH, WAKELING A: Bulimia nervosa: a placebo-controlled double-blind therapeutic trial of mianserin. *Brit. J. Clin. Pharmacol.* (1983) 15 (suppl):195S-202S.

335. NOBLE RE: Effect of cyproheptadine on appetite and weight gain in adults. *JAMA* (1969) 209:2054-2055.

336. SILVERSTONE T, SCHUYLER D: The effect of cyproheptadine on hunger, calorie intake and body weight in man. *Pychopharmacologia* (1975) 40:335-340.

337. GLOBISCH J: Appetitlosigkeit, nervositat und untergewicht. *Arztl. Praxis* (1979) 29:1877-1881.

338. JENSCHKE H: Zur behandlung von appetitlosigkeit und untergewicht bei alterspatienten. *Therapiewoche* (1979) 29:1877- 1881.

339. MARTINDALE: The extra pharmacopoeia. 29th edition. Reynolds JR (ed). The Pharmaceutical Press, London, (1989).

340. GOLDBERG SC, HALMI KA, ECKERT ED, CASPER R, DAVIS JM: Cyproheptadine in anorexia nervosa. *Brit. J. Psychiat.* (1979) 134:67-70.
Failure of a putative 5-HT$_{1C/2}$ receptor antagonist and appetite enhancer to exhibit clinical efficacy in anorexia nervosa.

341. VIGERSKY RA, LORIAUX DL: Anorexia nervosa. Vigersky R (ed). Raven Press, New York, (1977), pp143-161.

342. HALMI KA, ECKERT E, LA DU TJ, COHEN J: Anorexia nervosa: treatment efficacy of cyproheptadine and amitryptyline. *Arch. Gen. Psychiat.* (1986) 43:177-181.

343. CRISP AH, LACEY JH, CRUTCHFIELD M: Clomipramine and "drive" in people with anorexia nervosa: an inpatient study. *Brit. J. Psychiat.* (1987) 150:355-358.

344. McENTEE WJ, COOK TH: Serotonin, memory, and the aging brain. *Psychopharmacology* (1991) 103:143-149.

345. ALTMAN HJ, NORDY DA, OGREN SO: Role of serotonin in memory: Facilitation by alaproclate and zimeldine. *Psychopharmacology* (1984) 84:496-502.

346. FLOOD JF, CHERKIN A: Fluoxetine enhances memory processing in mice. *Psychopharmacology* (1987) 93:36-43.

347. STREK KI, SPENCER KR, DeNOBLE VJ: Manipulation of serotonin protects against an hypoxia-induced deficit of a passive avoidance response in rats. *Pharmacol. Biochem. Behav.* (1989) 33:241-244.

348. ALTMAN HJ, STONE WS, OGREN SO: Evidence for a possible functional interaction between serotonergic and cholinergic mechanisms in memory retrieval. *Behav. Neural. Biol.* (1987) 48:49-62.

349. NYETH A-L, BALLADIN J, ELGEN K, et al.: Behandling Med citalopram vid demens. Normalisering av DST. *Nordic Psykiatrisk Tidskrift* (1987) 41:423-430.

350. NYETH A-L, GOTTFRIES CG: The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A nordic multicentre study. *Br. J. Psychiat.* (1990) 157:894-901.

351. FUDGE JL, PERRY PJ, GARVEY MJ, KELLY MW: A comparison of the effect of fluoxetine and trazodone on the cognitive functioning of depressed patient. *J. Affective Disord.* (1990) 18:275-280.

352. MOSKOWITZ H, BURNS M: The effects on performance of two antidepressant, alone and in combination with diazepam. *Prog. Neuropsychopharmacol. Bio. Psychiat.* (1988) 12:783-792.

353. NICHOLSON AN, PASCOE PA: Studies on the modulation of the sleep-wakefulness

continuum in man by fluoxetine, a 5-HT uptake inhibitor. *Neuropharmacology* (1988) 27:597-602.

354. WEINGARTNER H, RUDORFER MV, BUCHSBAUM MS, LINNOILA M: Effects of serotonin on memory impairments produced by ethanol. *Science* (1983) 221:472-474.

355. MARTIN PR, ADINOFF B, ECKARDT MJ, STAPLETON JM, BONE GAH, RUBINOW DR, LANE EA, LINNOILA M: Effective pharmacotherapy of alcoholic amnesic disorder with fluvoxamine. *Arch. Gen. Psychiat.* (1989) 46:617-621.

356. ECKHARDT MJ, STAPLETON JM, RIO D, GEORGE DT, RAWLINGS RR, WEINGARTNER H, LINNOILA M: Interactions of fluvoxamine and ethanol in healthy volunteers. 15th Collegium Int. Neuropsychopharmacologium (1986) pp 55-57.

357. SALETU B, GRUNBERG J, RAJNA P, KAROBATH M: Clovoxamine and fluvoxamine: 2 biogenic amine reuptake inhibiting antidepressants: quantitative EEG, psychometric and pharmacokinetic studies in man. *J. Neural Transm.* (1980) 49:63-86.

358. CURRAN HV, LADER M: The psychopharmacological effects of repeated doses of fluvoxamine, mianserin and placebo in healthy human subjects. *Eur. J. Clin. Pharmacol.* (1986) 29:601-607.

359. BARTFAI A, ASBERG M, MARTENSSON B, GUSTAVSSON P: Memory effect of clomipramine treatment: Relationship to CSF monoamine metabolites and drug concentrations in plasma. *Biol. Psychiat.* (1991) 30:1075-1092.

360. HINDMARCH I, BHATTI JZ: Psychopharmacological effects of sertraline in normal, healthy volunteers. *Eur. J. Clin. Pharmacol.* (1988) 35:221-223.

361. CURRAN HV, SHINE P, LADER M: Effects of repeated doses of fluvoxamine, mianserin and placebo on memory and measures of sedation. *Psychopharmacology* (1986) 89:360-363.

362. HINDMARCH I, SHILLINGFORD J, SHILLINGFORD C: The effects of sertraline on psychomotor performance in elderly volunteers. *J. Clin. Psychiat.* (1990) 51:12 (suppl B):34-36.

363. ALTMAN HJ, NORMILE HJ: Enhancement of the memory of a previously learned aversion habit following pre-test administration of a variety of serotonergic antagonists in mice. *Psychopharmacology* (1986) 90:24-27.

364. NORMILE HJ, ALTMAN HJ: Enhanced passive avoidance retention following poststrain serotonergic receptor antagonist administration in middle-aged and aged rats. *Neurobiol. Aging* (1988) 9:377-382.

365. HAKKOU F, JAOUNEN C, IRAKI L: A comparative study of cyproheptadine and DL carnithine on psychomotor performance and memory in healthy volunteers. *Fundam. Clin. Pharmacol.* (1990) 4:191-200.

366. SEIBYL JP, KRYSTAL JH, PRICE LH, WOODS SW, HENINGER GR, CHARNEY DS: 5-HT function in the biochemical and behavioural responses to mCPP in healthy subjects and schizophrenics. *Am. Soc. Neurosci. Abstr.* (1989) 15:485.21.
•• First report that mCPP can induce psychosis in scizophrenics.

367. KRYSTAL JH, SEIBYL JP, PRICE LP, WOODS SWM, HENINGER GR, CHARNEY DS: MCPP effect in schizophrenic patients before and after typical and atypical neuroleptic treatment. *Schizophrenia Res.* (1991) 4:350.

368. IQBAL N, ASNIS GM, WETZLER S, KAHN RS, KAY S, VAN PRAAG HM: The mCPP challenge test in schizophrenia: Hormonal and behavioural responses. *Bio. Psychiat.* (1991) 30:770-778.

369. OWEN RR, GUTIERREZ L, HADD K, BENKELFAT C, MURPHY DL: Serotonergic responsivity in schizophrenia. *Am Psychiat. Assoc.* (1990) New Res Abstr: NR235.

370. KAHN RS, SIEVER LJ, GABRIEL S, AMIN F, STERN RG, DUMONT K, APTER S, DAVIDSON M: Serotonin function in schizophrenia: Effects of metachlorophenylpiperazine in schizophrenic patients and healthy subjects. *Psychiatry Res.* (1992) 43:1-12.

371. GELDERS Y, VAN DEN BUSSCHE G, REYNTJENS A, JANSSEN P: Serotonin S2 receptor blockers in the treatment of chronic schizophrenia. *Clin. Neuropharmacol.* (1986) 9:325-327.

372. GELDERS YG: Thymosthenic agents, a novel approach in the treatment of schizophrenia. *Brit. J. Psychiat.* (1989) 155 (suppl. 5):33-36.

373. SILVER H, BLACKER M, WELLER MPI, LERER B: Treatment of chronic schizophrenia with cyproheptadine. *Biol. Psychiat.* (1989) 25:502-504.

374. BERSANI G, GRISPINI A, PASINI MA, VALDUCCI M, CIANI N: 5-HT$_2$ antagonist ritanserin in neuroleptic-induced parkinsonism: a double-blind comparison with orphenadrine and placebo. *Clin. Neuropharmacol.* (1990) 13:500-506.

375. MAERTENS DE NOORDHOUT A, DELWAIDE PJ: Open pilot trial of ritanserin in Parkinson's disease. *Curr. Therap. Res.* (1986) 9:480-484.

376. MECO G, MARINI S, LESTING L, L'INFANTE 1, MODARELLI F, AGNOLI A: Controlled single-blind cross-over study of ritanserin and placebo in l-DOPA-induced dyskinesias in Parkinson's disease. *Curr. Therap. Res.* (1988) 43:262-270.

377. MILLER CH, FLEISHACKER WW, EHRMANN H, KANE JM: Treatment of neuroleptic induced akathisia with the 5-HT$_2$ antagonist ritanserin. *Psychopharmacol. Bull.* (1990) 26:373-376.

378. MELTZER HY: Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. *Psychopharmacology* (1989) 99:S18-S27.
•• Proposal that 5-HT$_2$ receptor antagonist efficacy was

important to the improved profile of atypical antipsychotic drugs.

379. CANTON H, VERRIELE L, COLPAERT FC: **Binding of**
• **typical and atypical antipsychotics to 5-HT$_{1C}$ and 5-HT$_2$ sites: clozapine potently interacts with 5-HT$_{1C}$ sites.** Eur. J. Pharmacol. (1990) 191:93-96.
Proposal that 5-HT$_{1C}$ receptors may mediate the improved side effect profile and efficacy against negative symptoms of 'atypical' antipsychotic drugs.

380. ROTH BL, CIARANELLO RD, MELTZER HY: **Binding of**
•• **typical and atypical antipsychotic agents to transiently expressed 5-HT$_{1C}$ receptors.** J. Pharmacol. Exp. Therap. (1990) 260:1361-1365.
Refutation of the hypothesis that 5-HT$_{1C}$ receptors mediate the improved side effect profile and efficacy against negative symptoms of atypical antipsychotic drugs.

381. CEULEMANS DLS, GELDERS YG, HOPPENBROUWERS M-L, et al.: **Effect of serotonin antagonism in schizophrenia: a pilot study with setoperone.** Psychopharmacology (1985) 85:329-332.

382. HARNRYD C, BJERNSTADT L, GULLBERG B: **A clinical comparison of melperone and placebo in schizophrenic women on a milieu therapeutic ward.** Acta. Psych. Scand. Suppl. (1989) 352:40-47.

383. CHRISTENSSON EG: **Pharmacological data of the atypical neuroleptic compounds melperone.** Acta. Psychiat. Scand. Suppl. (1989) 352:7-15.

384. GUNNE LM, JOHANSSON P: **Chronic melperone administration does not induce oral movements in rats.** Acta. Psychiat. Scand. Suppl. (1989) 352:48-50.

385. SVARTENGREN J, SIMONSSON P: **Receptor binding properties of amperozide.** Pharmacol. Toxicol. (1990) 66 (suppl 1):11.

386. ALBINSSON A, ERIKSSON E, ANDERSSON G: **Amperozide-effect on prolactin release in the rat.** Pharmacol. Toxicol. (1990) 66 (suppl 1):49-51.

387. CHRISTENSSON EG, BJORK A: **Amperozide: a new pharmacological approach in the treatment of schizophrenia.** Pharmacol. Toxicol. (1990) 66 (suppl 1):5-7.

388. ANDERSON GM, HORNE WC, CHATTERJEE D, COHEN DJ: **The hyperserotonemia of autism.** Ann. N. Y. Acad. Sci. (1990) 600:331- 340.

389. CLINESCHMIDT BV, ZACCHEI AG, LOTARO JA, PFLUEGER AB, MCGUFFIN JC, WISHOUSKY TI: **Fenfluramine and brain serotonin.** Ann. N. Y. Acad. Sci. (1978) 305:222-241.

390. GELLERE E, RITVO ER, FREEMAN BJ, YUWILER A: **Preliminary observations on the effect of fenfluramine on blood serotonin and symptoms in three autistic boys.** N. Engl. J. Med. (1982) 307:165- 169.

391. AMAN MG, KERN RA: **Review of fenfluramine in the treatment of the developmental disabilities.** J. Am. Acad. Child Adolesc. Psychiat. (1989) 28:549-565.

392. FISH B, CAMPBELL M, SHAPIRO T, FLOYD A: **Schizophrenic children treated with**
methysergide (Sansert). Dis. Nerv. Syst. (1969) 30:534-540.

393. PRANZATELLI MR, MURTHY JN, PLUCHINO RS: **Identification of spinal 5-HT$_{1C}$ binding sites in the rat: characterization of [^{3}H]mesulergine binding.** J. Pharm. Exp. Ther. (1992) 261:161-165.

394. HARRIS GD, ZEMLAN FP, MURPHY RM, BEHBEHANI MM: **Spinal cord 5-HT, 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes: relation to pain transmission** neurosci. Abstr. (1986) 12:1015.

395. ZEMLAN FP, BEHBEHANI MM, MURPHY RM: **Serotonin receptor subtypes and the modulation of pain transmission.** Prog. in Brain Res. (1988) 77:349-355.

396. MCKEARNEY JW: **Apparent antinociceptive properties of piperazine-type serotonin agonists: Trifluoromethylphenylpiperazine, chlorophenylpiperazine, and MK-21.** Pharmacol. Biochem. Behav. (1989) 32:657-660.

397. SANDRINI G, ALFONSO E, DE RYSKY C , MARINI S, FACCHINETTI F, NAPPI G: **Evidence for serotonin-S2 receptor involvement in analgesia in humans.** Eur. J. Pharmacol. (1986) 130:311-314.

398. SZELE FG, MURPHY DL, GARRICK NA: **Effects of**
• **fenfluramine, m- chlorophenylpiperazine, and other serotonin-related agonists and antagonists on penile erections in non human primates.** Life Sci. (1988) 43:1297-1303.
MCPP observed to cause penile erection in primates.

399. BARALDI M, BENASSI-BENELLI A, LOLLI M: **Penile erections in rats after fenfluramine administration.** Riv. Farmacol. Ther. (1977) 8:375-379.

400. BERENDSEN HHG, BROEKKAMP CLE: **Drug-induced penile erections in rats: indications of serotonin 1B receptor mediation.** Eur. J. Pharmacol. (1987) 135:279-287.

401. KRANE RJ, GOLDSTEIN I, SAENZ DE TEJADA I: **Impotence.** N. Engl. J. Med. (1989) 321:1648-1649.

402. BAHOS JE, BOSCH F, FARRE M: **Drug-induced priapism. Its aetiology, incidence and treatment.** Med. Toxicol. Adverse Drug Exper. (1989) 4:46-58.

403. CSERR HF: **Physiology of the choroid plexus.** Physiol. Rev. (1971) 51:273-311.

404. DAVSON H, WELCH K, SEGAL MB: **The physiology and pathophysiology of the cerebrospinal fluid.** Churchill Livingstsone, New York (1987).

405. LINDVALL-AXELSSON M, MATHEW C, NILSSON C, OWMAN C: **Effect of 5-hydroxytryptamine on the rate of cerebrospinal fluid production in rabbit.** Exp. Neurol. (1988) 90:362-268.

406. MAEDA K: **Monoaminergic effects on cerebrospinal fluid production.** Nihon Univ. J. Med. (1983) 25:155-174.

407. VAN NUETEN JM, JANSSENS WJ, VANHOUTTE PM: **Serotonin and vascular smooth muscle.** Vanhoutte PM (Ed). Raven Press, New York (1985).

408. DROPP JJ: Mast cells in the central nevous system of several rodents. *Anat. Rec.* (1972) 174:227-233.

409. EDVINSSON L, LINDVALL M: Autonomic vascular innervation and vasomotor reactivity in the choroid plexus. *Exp. Neurol.* (1978) 62:394-404.

410. MOSKOWITZ MA, LIEBMANN JE, REINHARD JF, SCHLOSBERG A: Raphe origin of serotonin-containing neurons within the choroid plexus of the rat. *Brain Res.* (1979) 169:590-594.

411. NAPOLEONE P, SANCESARIO G, AMENTA F: Indoleaminergic innervation of rat choroid plexus: a fluorescence histochemical study. *Neurosci. Lett.* (1982) 34:143-147.

412. LOREZ HP, RICHARDS JG: 5-HT nerve terminals in the fourth ventricle of the rat brain: their identification and distribution studied by fluorescence microscopy. *Cell Tissue Res.* (1975) 165:37-34.

413. MATSUURA T, TAKEUCHI Y, KOJIMA M, UEDA S, YAMADA H, NOJYO Y, USHIJIMA K, SANO Y: Immunohistochemical studies of the serotonergic supraependymal plexus in the mammalian ventricular system, with special reference to the characteristic reticular ramificiation. *Acta Anat.* (1985) 123:207-219.

414. SKARSFELDT T, LARSEN JJ: SCH 34490 - a selective dopamine D_1 receptor antagonist with putative 5-HT$_1$ receptor agonistic activity. *Eur. J. Pharmacol.* (1988) 148:389-395.

415. BOYSON SJ, MCGONIGLE P, MOLINOFF PB: Quantitative autoradiographic localisation of the D_1 and D_2 subtypes of dopamine in the rat brain. *J. Neurosci.* (1986) 6:3177-3188.

416. BOYSON SJ, ALEXANDER A: Net production of cerebrospinal fluid is decreased by SCH-34490. *Ann. Neurol.* (1990) 27:631-635.

417. TURCONI M, SCHIANTARELLI P, BORSINI F, RIZZI CA, LADINSKY H, DONETTI A: Azabicycloalkyl benzimidazolones: interaction with serotonergic 5-HT$_3$ and 5-HT$_4$ receptors and potential therapeutic implications. *Drugs of the Future* (1991) 16:1011-1026.

418. CARR AA, HAY DA, DUDLEY MW, NIEDUZAK TR: Derivatives of MDL 11939 as highly potent and selective inhibitors of serotonin 5-HT$_2$ receptors. Abstract 180, *The Second IUPHAR Satellite Meeting on Serotonin.* Basel, Switzerland, July 1990. Abs 180
Report of the development of very selective 5-HT$_2$ receptor antagonists.

419. COHEN ML, WITTENAUER LA: Further evidence that the serotonin receptor in the rat stomach fundus is not 5-HT$_{1A}$ or 5-HT$_{1B}$. *Life Sci.* (1986) 38:1-5.

420. TEICHER MH, GLOD C, COLE JO: Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am. J. Psychiat.* (1990) 147:207-210.

421. LEBEGUE BJ: Sudden self harm while taking fluoxetine. *Am. J. Psychiat.* (1992) 149:1113.

422. DOWNS J, WARD J, FARMER R: Preoccupation with suicide in patients treated with fluoxetine. *Am. J. Psychiat.* (1991) 148:1090-1092.

423. HOYER D, FOZARD JR: Receptor data for biological experiments: a guide to drug selectivity. Doods HN, Van Meel JCA, (Eds). Ellis Horwood series in biological sciences, New York, (1991), pp 35-41.

424. HOYER D: Functional correlates of serotonin 5-HT1 recognition sites. *J. Recept. Res.* (1988) 8:59-81.

425. ZGOMBICK JM, SCHECHTER LE, MACCHI M, HARTIG PR, BRANCHEK TA, WEINSHANK RL: Human gene S31 encodes the pharmacologically defined serotonin 5-hydroxytryptamine $_{1E}$ receptor. *Mol. Pharmacol.* (192) 42:180-185.

426. BAGDY G, SZEMEREDI K, KANYICSKA B, MURPHY DL: Different serotonin receptors mediate blood pressure, heart rate, plasma catecholamine and prolactin responses to m- chlorophenyl-piperazine in conscious rats. *J. Pharm. Exp. Ther.* (1989) 250:72-78.

427. KLODZINSKA A, JAROS T, CHOJNACKA-WOJCIK E, MAJ J: Exploratory hypoactivity induced by m-trifluoromethylphenylpiperazine (TFMPP) and m-chlorophenylpiperazine (mCPP). *J. Neural. Trans.* (1989) 1:207- 218.

428. SAMANIN R, MENNINI T, FERRARIS A, BENDOTTI C, BORSINI F, GARATTINI S: m-Chlorophenyl-piperazine: a central serotonin agonist causing powerful anorexia in rats. *Naunyn-Schmiedebergs Arch. Pharmacol.* (1979) 308:159-163.

429. FULLER RW, SNODDY HD, MASON NR, OWEN JE: Disposition and pharmacological effects of mCPP. *Neuropharmacology* (1981) 20:155- 162.

430. KLODZINSKA A, CHOJNACKA-WOJNIK E: Anorexia induced by m- trifluoromethylphenyl-piperazine (TFMPP) in rats. *Pol. J. Pharmacol.* (1990) 42:13-17.

431. STEWART BR, JENNER P, MARSDEN CD: Induction of purposeless chewing behaviour in rats by 5-HT agonist drugs. *Eur. J. Pharmacol.* (1989) 162:101-107.

432. PIERCE PA, PEROUTKA SJ: Hallucinogenic drug interactions with neurotransmitter receptor binding sites in human cortex. *Psychopharmacology* (1989) 97:118-122.

Referenc s to pat nt lit rature:

500. SMITHKLINE BEECHAM PHARMACEUTICALS, WO 92/05170 (1991)

501. SANDOZ LTD., EP-473-550-A1 (1991)

502. ELI LILLY AND COMPANY, EP-449-561-A2 (1991).